

**Quantifying the Patient Population of Ultra-Orphan Diseases: a Case Study in X-Linked Hypohidrotic Ectodermal Dysplasia**

by

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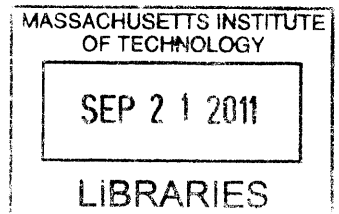
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# Abstract

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Quantifying the Patient Population of Ultra-Orphan Diseases: a Case Study in X-Linked Hypohidrotic Ectodermal Dysplasia

by

Julie Hermann

Submitted to the Harvard-MIT Division of Health Sciences and Technology in partial fulfillment of the requirements for the degree of Masters in Science in Health Sciences and Technology

Understanding the true incidence and prevalence of a disease has tremendous value for the biopharmaceutical industry, particularly for orphan diseases that affect a minority of the population (in the US, the definition of orphan disease is a disorder that must affect less than 200,000 people, or 1 in 1,500). However, incidence and prevalence data for orphan diseases in scientific literature is poorly studied, inconsistent, numbers range widely and articles often contain poorly supported citations. Additionally, once a treatment is available and disease awareness increases, there may be an increase in reported disease prevalence, as patients proactively seek treatment from their healthcare providers.

The goal of this research is to investigate the incidence of X-linked Hypohidrotic Ectodermal Dysplasia (XLHED) and provide a framework for investigators to study the incidence and prevalence of other rare diseases. Specific research objectives include:

- 1) Develop a clinical phenotype to identify XLHED patients in medical records and/or claims data
- 2) Analyze patient registry data to identify characteristics that are unique to XLHED and distinguish XLHED from other ectodermal dysplasias
- 3) Develop a robust search algorithm to accurately identify XLHED patients in claims databases

By performing a thorough literature review, and an analysis of the National Foundation for Ectodermal Dysplasias (NFED) patient registry, I was able to meet the first two research objectives. After analyzing the medical record and claims data at two major academic medical centers, we were only able to identify 25 total patients, 19 of whom had associated claims data, to include in our patient cohort. Since this number was too small of a base from which to develop an identification algorithm as originally planned, I instead analyzed descriptive statistics of their claims data in order to better understand how these patients flow through the healthcare system, and what identification criteria might be valuable for an investigator studying a larger patient population in the future.

Further studies using different combinations of claims and/or narrative data to more accurately identify HED patients and therefore increase the sample size of future analyses are recommended to continue this epidemiological research and provide new insights into the diagnosis and treatment patterns of XLHED.

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# Introduction

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## **X-Linked Hypohidrotic Ectodermal Dysplasia**

X-Linked Hypohidrotic Ectodermal Dysplasia (XLHED) is a disease characterized by a reduction or absence in sweat glands, thin and sparse hair, and missing teeth. The gene affected in XLHED (EDA, OMIM 305100) is located on the X chromosome; therefore, the full features of the disease are present in male patients, while the heterozygous female patients demonstrate a milder form of the disease. Severity of the disease in males is variable, with some correlation between the specific location of the genetic mutation and the resulting phenotype.

The epidemiology of XLHED has not been thoroughly studied, and estimates of disease incidence and mortality vary widely in the literature. Quoted incidence rates range from 1 in 10,000 to 1 in 100,000 births<sup>1</sup>, and mortality estimates range from 2% to 30%<sup>2</sup> infants. Research methods used in these studies are poorly documented and geographically biased. Examples of prevalence studies in the literature include an investigator sending letters to all pediatricians, dermatologists, and geneticists in Wales, and subsequently visiting the families at home to collect data<sup>3</sup>. Another investigator initiated his study by sending letters to all orthodontists, prosthodontists, and oral surgeons in Norway in order to identify patients<sup>4</sup>.

## **Research Goals and Methods**

Understanding the true incidence and prevalence of a disease has tremendous value for the biopharmaceutical industry, particularly for orphan disorders, which affect only a minority of the population (a disorder must affect less than 1 in 1,500 people to qualify for orphan status in the US). However, disease epidemiology is critical when potential investors or biopharmaceutical companies are attempting to estimate the market opportunity in a therapeutic area or value a potential drug candidate.

At the time of an investment decision, it is important to have an accurate understanding of the incidence and prevalence of a disease to understand a potential determine the market size and revenue potential. Not only are patient numbers important in themselves, but the disease epidemiology can also



inform pricing potential, since the lower the prevalence of a disease being treated by an orphan drug, the higher a price a drug can generally demand.

As a drug approaches commercialization, detailed prevalence data provides further information on market structure, which is important in developing marketing strategies and forecasting market share. In addition, accurate demand forecasting to ensure adequate levels of the drug are produced at the time of launch to ensure all patients are able to be treated and to prevent any loss in sales, while at the same time minimizing inventory costs of keeping adequate stock on hand.

However, incidence and prevalence data for orphan diseases in the published literature is inconsistent – estimates range widely from paper to paper, and articles often contain poorly supported citations. Epidemiological studies of orphan diseases are often geographically biased, and the smaller the region studied, the more likely that the estimated prevalence will be much higher or lower than the actual disease prevalence. Additionally, once a treatment is available and, subsequently, awareness of the disease increases, there may be an increase in the prevalence of the disease, as more patients proactively seek treatment from their healthcare providers. Finally, rates of misdiagnosis and underdiagnosis, early mortality in untreated patients, and reproductive decisions of carriers all affect reported incidence, and all may also change when a treatment becomes available.

The goal of this research is to investigate the incidence of X-linked Hypohidrotic Ectodermal Dysplasia (XLHED) and provide a framework for investigators to study the incidence and prevalence of other rare diseases. Specific research objectives include:

- 1) Develop a clinical phenotype that is expected to identify XLHED patients in medical records and/or claims data
- 2) Analyze patient registry data to identify specific characteristics that are unique to XLHED and distinguish XLHED from other ectodermal dysplasias
- 3) Develop a robust search algorithm to accurately identify XLHED patients in large claims databases.

Planned research methods include:

- 1) A thorough literature review, to outline what studies have been completed to show disease incidence and prevalence, as well as to identify common symptoms that can be used in the identification algorithm
- 2) Analysis of an XLHED patient registry, to further develop the patient profile for this disease that will be used as inclusion criteria in the identification algorithm
- 3) Analysis of an electronic data repository containing both electronic medical records (EMRs) and claims data
- 4) Creation of an identification algorithm using claims data for the inclusion and exclusion criteria

The goal of the algorithm is that it could be later applied to a large claims database in order to estimate the disease incidence and prevalence in the US population.

# Literature Review

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## Methodology

To understand the recognized symptoms and treatment patterns of XLHED patients, I conducted an extensive review of scientific journals by searching PubMed across a variety of terms – related to the disease (X-Linked Hypohidrotic Ectodermal Dysplasia, Hypohidrotic Ectodermal Dysplasia, Ectodermal Dysplasia), epidemiological methods (incidence or prevalence studies, electronic medical records, claims databases), and orphan diseases in general. I studied the disease etiology and genetics, published incidence rates, methods of diagnosis, common clinical features, as well as available treatment options. From this research, in conjunction with the registry analysis, I was able to develop a profile of a typical XLHED patient, which could be used to inform potential inclusion criteria for an identification algorithm. In addition, I researched methods that had been used by researchers for other diseases to study incidence and prevalence rates, or other epidemiological studies using electronic medical records and claims databases.

There were limitations in generating analysis from existing scientific literature. First, there was a low level of consistency in the results of studies estimating disease incidence and prevalence. Incidence rates varied from a high of 7 in 10,000<sup>5</sup> to a low of 1 in 100,000<sup>6</sup>, which given a US population of approximately 307 million citizens. Based on these broad assumptions, one could conclude that the US prevalence of the disease might range anywhere from 3,000 to 215,000 patients.

In addition, many of the studies are geographically biased – only patients within a particular region were studied. These studies also required either a physician or a patient to opt-in to be included in the research. For example, in a study conducted by Clarke in the 1980s, the investigator contacted all pediatricians and dermatologists in Wales to request permission to contact patients who fit the clinical profile of XLHED<sup>3</sup>, and in a study conducted in 2003, the investigators contacted all orthodontists, prosthodontists, and oral surgeons in Norway to identify patients to participate.<sup>4</sup>

## Ectodermal Dysplasia

XLHED is one disorder within the family of Ectodermal Dysplasias (ED), a group of approximately 200 diseases affecting tissues of ectodermal origin, including the teeth, the epidermis and appendages, the nervous system, and sensory organs. To qualify as ED, a disease must cause abnormal development in at least one of the classic ectodermal structures – hair (hypotrichosis, partial, or total alopecia), nails (dystrophic, hypertrophic, abnormally keratinized), teeth (enamel defect or absent), or sweat glands (hypoplastic or aplastic) – as well as either a second defect in one of the classic structures or a defect in one of the other ectodermal structures – ears, lips, or dermatoglyphics on the palms or the soles of the feet.<sup>5</sup> The full list of possible clinical features in the Ectodermal Dysplasia family of disorders is listed in Table 1.

**Table 1: Clinical Features in Ectodermal Dysplasias<sup>5</sup>**

<p>Skin alteration</p> <ul style="list-style-type: none"> <li>Superficial dry scaling skin at birth</li> <li>Dry and often hypopigmented skin</li> <li>Dermatitis resembling atopic skin disease</li> </ul> <p>Impaired sweat gland function</p> <ul style="list-style-type: none"> <li>Absence or reduction of sweating</li> <li>Hyperthermia under warm condition</li> </ul> <p>Abnormalities in hair follicles</p> <ul style="list-style-type: none"> <li>Sparse, curly, and fair hair</li> <li>Alopecia because of hypotrichosis or increased hair fragility</li> <li>Eyebrows or eyelashes absent/sparse or malformed</li> </ul> <p>Nail changes</p> <ul style="list-style-type: none"> <li>Leukonychia</li> <li>Dystrophic and malformed nails</li> </ul> <p>Dental changes</p> <ul style="list-style-type: none"> <li>Hypodontia or anodontia</li> <li>Malformed teeth with cone- or pegshaped aspect</li> <li>Prone to caries because of enamel defect or salivary gland malfunction with xerostomia</li> </ul> <p>Facial changes</p> <ul style="list-style-type: none"> <li>Dysmorphic features</li> <li>Numerous facial malformations</li> </ul>
--

#### Eye abnormalities

- Corneal dysplasias
- Cataract
- Displaced or stenotic lacrimal puncta
- Defective or decreased lacrimation

Approximately 80% ED cases are classified as hypohidrotic ectodermal dysplasias (HED)<sup>6</sup>. The specific forms of HED are caused by mutations in different genes but lead to the same classic phenotypic features – absent/abnormal teeth, sparse/thin hair, and lack of ability to sweat. XLHED is the most common form of HED (estimated to be between 75%-95% of cases<sup>7,8</sup>), and is caused by a mutation in the EDA (ectodysplasin-A) gene. Other forms of HED include autosomal recessive and autosomal dominant forms, which are caused by mutations in the EDAR (ectodysplasin-A receptor) and EDARADD (ectodysplasin-A receptor-associated adapter protein) genes.<sup>7</sup>

## Disease History

Reports of XLHED date back to Charles Darwin, who reported in 1875 of an Indian family with abnormal hair and teeth. Darwin noted that the disease only affected the sons of the family, and speculated that the disease was transmitted through the female carriers, hinting at the recessive nature of XLHED.<sup>9</sup> In 1913, the disease was described as a congenital ectodermal defect by Christ, and termed as anhidrotic ectodermal dysplasia by Weech in 1929 due to the decreased sweat gland function. Finally, in 1944, Felsher changed its name from anhidrotic to hypohidrotic ectodermal dysplasia, since the skin of affected patients is rarely completely anhidrotic.<sup>1</sup> Mutations of the EDA have also been reported in cows, dogs, and mice.<sup>10</sup>

## Etiology & Genetics

XLHED is caused by a mutation in the EDA1 gene. EDA1 codes for ectodysplasin-A, a member of the tumor necrosis family of proteins required for the development of the ectodermal appendages. The EDA gene consists of 12 exons, 8 of which encode the protein ectodysplasin A. Ectodysplasin A consists of three critical areas – an extracellular protein cleavage site, a collagen domain, and a TNF homology domain. XLHED can be caused by a mutation in any of these three domains.<sup>11</sup> More than sixty mutations have been identified in the EDA gene, including nucleotide substitutions, small deletions, gross deletions, and small insertions.<sup>7</sup>

During normal embryogenesis, the EDA ligand binds to the EDAR receptor, which recruits the EDARADD protein and causes the activation of the NF- $\kappa$ B transcription factor.<sup>1</sup> Mutations in the genes that code for the EDAR and EDARADD proteins are responsible for the autosomal dominant and recessive versions of HED. Since all three are required for normal ectodermal development, a defect in the EDA, EDAR, or EDARADD genes will result in a similar phenotypic expression.

The primary purpose of the NF- $\kappa$ B transcription pathway is to produce inflammatory and immune responses, as well as to regulate apoptosis. During embryogenesis, the EDA gene controls cell survival and differentiation of the ectodermal tissues through the NF- $\kappa$ B transcription pathway.<sup>5</sup> In addition to causing the classic HED symptoms, the deficiencies in this pathway can also result in immune deficiencies, osteoporosis, and lymphedema.<sup>10</sup>

## Cardinal Features

There are three cardinal clinical features of XLHED: hypotrichosis (sparseness of hair), hypohidrosis (reduced ability to sweat), and hypodontia (absence of or abnormal teeth). XLHED patients often have thin, light-colored scalp and body hair which grows more slowly than normal hair. However, secondary hair, such as facial or pubic hair, is often normal.<sup>7</sup>

Patients with XLHED have a reduced ability to sweat, caused by a reduction in the number of sweat glands. This can often lead to hypothermia, and must be closely managed during infancy and childhood to prevent seizures that could result in neurological damage.<sup>5</sup> The absence of sweat glands also causes extreme dryness of the skin, or eczema.<sup>1</sup>

XLHED patients also have multiple missing and/or abnormal teeth. The average XLHED patient has only 5 - 9 permanent teeth<sup>1,11</sup>, usually the canines and first molars. The teeth that are present are often smaller than normal teeth, and conical or peg shaped.<sup>7</sup> See Figure 1 for the classic dental presentation of a child with HED. Other dental abnormalities include underdeveloped enamel, which can increase the risk for cavities and tooth decay. One study also found taurodontism to be common among XLHED patients, a condition in which the tooth body and pulp chamber are enlarged at the expense of the root.<sup>11</sup>

**Figure 1: Dental presentation of XLHED in a child<sup>1</sup>**

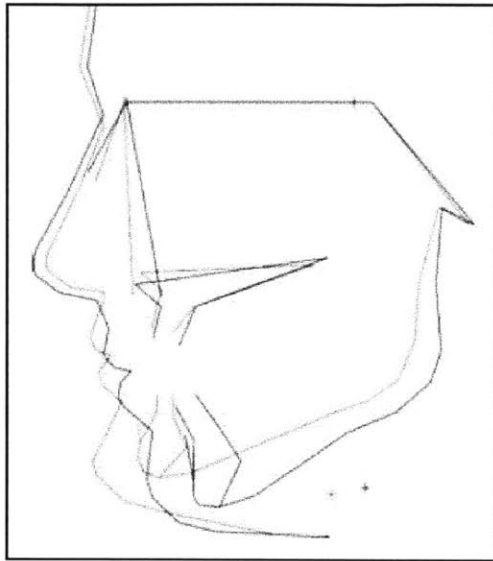


A form of XLHED, X-Linked Recessive Hypodontia (XLRH), is also caused by a mutation in the EDA gene. However, due to the location of the mutations, XLRH patients only suffer one of the cardinal features – missing and abnormal teeth. XLRH is caused by missense mutations in the TNF homology domain of Ectodysplasin A. Unlike XLHED, which cause complete loss of binding from EDA ligand to the EDAR receptor protein, the mutations causing XLRH do not completely inhibit binding of the ligand and receptor, and sufficient signaling still occurs for sweat gland and hair development. In addition, while patients with XLRH experience dental abnormalities, they are generally not as severe as those typically experienced by XLHED patients. However, given their similarities in genotypic and phenotypic similarities, XLRH is considered a milder type of XLHED.<sup>12</sup>

### **Other Clinical Characteristics**

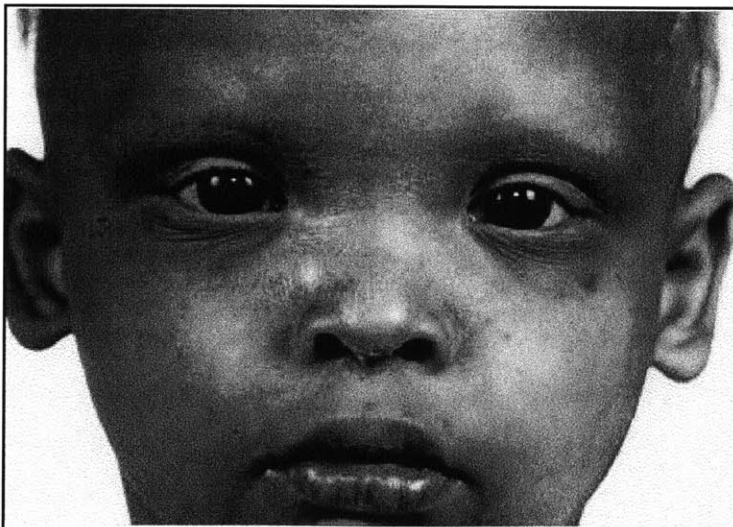
Many XLHED patients have feeding problems and experience failure to thrive in infancy. During adolescence, XLHED patients tend to have a lower than average body mass index and weight, although they are generally of normal height.<sup>3</sup> The average head circumference of XLHED patients is smaller than those of normal controls, and XLHED patients have been found to also have a shorter maxillary bone, retroclined nasal bone, and anteriorly inclined mandible. See Figure 2 for a comparative tracing of male XLHED and male controls.<sup>13</sup>

**Figure 2: Tracing of XLHED males (red) superimposed on male controls (black)<sup>13</sup>**



XLHED patients tend to have a short head height, prominent forehead, and high-set eye sockets.<sup>14</sup> Their faces are characterized by a short, saddle-shaped nose; large, protruding lips;<sup>13</sup> as well as wrinkling and hyperpigmentation around the eyes.<sup>1</sup> They tend to have less subcutaneous fat than normal, resulting in skin that appears thin and fragile. They also lack dermal ridges on their fingers, palms, and the soles of their feet.<sup>7</sup> See Figure 3 for facial characteristics of an XLHED patient.

**Figure 3: Facial characteristics of XLHED: sparse scalp/eyebrow/eyelash hair, depressed nose, periorbital pigmentation, protruding lips<sup>15</sup>**



XLHED patients experience abnormal gland development, leading to missing or diminished mucous glands in their respiratory and gastrointestinal tracts. As a result of this deficiency, many patients suffer from wheezing and asthma, a raspy voice, and are at an increased risk for recurrent respiratory infections.<sup>3,7</sup> In addition to decreased mucus production, XLHED patients usually experience decreased production of all bodily fluids, including saliva and tears.<sup>3</sup>

## Diagnosis

A diagnosis of XLHED is generally made after infancy based on the classic features of the disease – the lack of sweat glands causing hyperpyrexia, the lack of hair or presence of thin/sparse hair, and either the absence of teeth or presence of conical/peg-shaped teeth. These features can be difficult to detect in infancy, making early diagnosis uncommon unless the family is aware of a mother's carrier status. Early clues for diagnosis of neonates may include peeling skin at birth, eczema, periorbital hyperpigmentation, frequent respiratory infections, or allergies. Most infants are not diagnosed until after the age of 6-9 months, when the first teeth fail to erupt.<sup>1,7</sup> Genetic testing is required to confirm diagnosis of XLHED, since all forms of HED are phenotypically similar.

Prenatal diagnosis is also possible for high-risk pregnancies. A DNA test can be administered on fetal cells obtained by chorionic villus sampling at ten to twelve weeks gestation, or amniocentesis at fifteen to eighteen weeks.<sup>7</sup> In addition, a fetoscopy-guided skin biopsy can be taken during the second semester for histology analysis.<sup>16</sup>

Certain features of the disease can also be detected by ultrasound. Using 2D ultrasound, it is possible to evaluate major defects related to the disease, including facial clefts, cyclopia, and orbital abnormalities (see Figure 4). Additional clues are available using 3D ultrasound, including the characteristic protruding lips and decreased number of tooth buds (see Figure 5). Currently, use of 3D ultrasound is restricted to the third semester, when these features are easier to detect. However, as the 3D image resolution improves, it may be possible to diagnose the disease earlier in pregnancy.<sup>16</sup>



**Figure 4: 2D ultrasound of an XLHED fetus showing the characteristic prominent lips<sup>16</sup>**



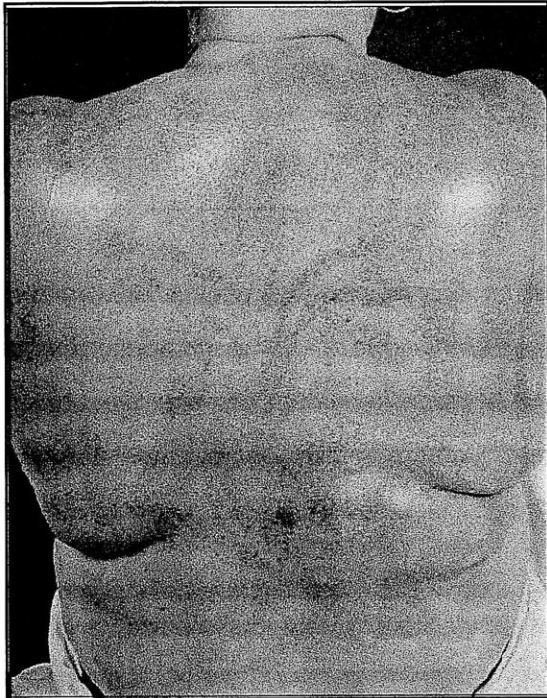
**Figure 5: 3D ultrasound of an XLHED fetus showing prominent lips and small nose<sup>16</sup>**



Carriers can be detected based on physical appearances, as they usually experience a milder form of the cardinal features of XLHED. Female carriers frequently demonstrate mosaic patterns of sweat pore distribution and function. Sweat gland function can be tested by applying an iodine solution to the skin and increasing the temperature to cause sweating. When iodine comes in contact with sweat, it

changes color. Therefore, patterns of color change can be used to determine the presence and location of sweating. The patterns of sweat gland presentation often fall along lines of Blaschko, and follow a V shape across the back; a wavy pattern on top of the head, and an S shape over the chest, stomach, and sides.<sup>5</sup> See Figure 6 for an example of sweat gland presentation along lines of Blascho. Carriers also frequently suffer from some degree of hypodontia and sparse hair. They may also experience deficient milk production when nursing due to abnormal glandular development.<sup>7,17</sup>

**Figure 6: Results of iodine testing on XHLED carrier showing sweat glands falling along Blascho lines<sup>17</sup>**



## **Treatment**

The primary XLHED symptom that needs immediate treatment at an early age is temperature management, since XLHED patients lack sweat glands to maintain temperature on their own. Patients are able to manage this condition by controlling their temperature externally – using techniques such as avoiding warm environments, keeping hydrated, utilizing air conditioners, or wearing wet clothing or cooling vests. Because XLHED patients often have less subcutaneous fat, they may also suffer in extremely cold climates and must take caution in colder temperatures as well.<sup>1</sup>

In order to correct dental abnormalities, XLHED patients either utilize dentures or dental implants. Dental implants are generally recommended after the age of seven, and must be replaced every two and

a half years during childhood<sup>7</sup>. Approximately a quarter of dental implants fail, which may be due to the lack of development in the alveolar ridge, or by bone structure hypermineralization, which can cause the mandibular cortex to be thicker and more difficult to drill through.<sup>18</sup> Patients unable to utilize implants can choose to utilize dentures as an alternative. Peg-shaped teeth may also be bonded to improve chewing ability and cosmetic appearance. Saliva substitutes and fluoride treatments can be administered to counter the lack of saliva in order to prevent cavities and dental decay and to improve feeding and digestion.<sup>7</sup>

Respiratory and gastrointestinal issues that are caused by a lack of mucosal glands are managed by treating and preventing infections. Most XLHED patients also receive standard treatments for asthma and eczema.<sup>1</sup> Finally, some XLHED patients choose to utilize a wig or special hair treatments to cope with thin and sparse scalp and body hair.<sup>7</sup>

## Registry Analysis

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### Methodology

The National Foundation for Ectodermal Dysplasias (NFED) maintains the Ectodermal Dysplasias International Registry, with the primary purpose to help clinicians and researchers to conduct analysis and design clinical trials for Ectodermal Dysplasia disorders. The de-identified, aggregated clinical data is available at the NFED's research portal (<http://nfed.researchcrossroads.org/>), and was accessed on March 7, 2011 for this study. At this time, 750 patients and their families had enrolled in the registry and completed an extensive questionnaire. Of these 750 entries, there were 164 male patients who reported a diagnosis of XLHED, and 254 male patients who reported a diagnosis of some form of HED. Subject areas captured by the registry included in this analysis are:

- Family History
- Diagnosis
- Growth & Development
- Limb/Finger/Toe Health
- Hair/Skin/Nail Health
- Eye/Vision Health

- Ear/Nose/Throat Health
- Oral/Dental Health
- Respiratory Health
- Allergy
- Digestive System
- Kidney/Bladder/Urination Health
- Reproductive Health
- Quality of Life

In order to refine the patient profile developed through the literature review and identify clear traits that could be incorporated as inclusion criteria in the identification algorithm, I looked at three patient populations that responded to the survey. I was able to filter by disease type and gender to see only the patient populations relevant for this research. In addition, I contacted the Director of Research at the NFED to gain de-identified, non-aggregated data for specific populations in order to identify trends at the patient level.

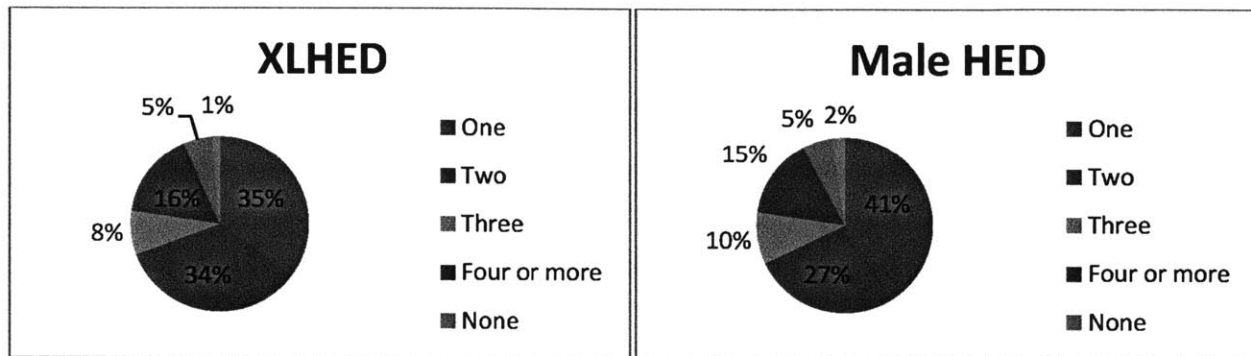
I first looked at the data filtered for male XLHED patients to pinpoint disease-specific traits. Since all genetic variants of HED are phenotypically similar, and it would be very difficult to distinguish between these specific disorders, I analyzed the data for all male patients diagnosed with some form of HED. Utilizing this larger population in conjunction with the XLHED patient cohort allowed me to test the sensitivity of the XLHED statistics and to have a broader sample size from which to identify trends. Finally, I reviewed the aggregated data for ED patients that were diagnosed with a disorder other than HED in order to identify potential exclusion criteria that could distinguish patients whose claims data also contained the ICD-9 code 757.31 (the diagnosis code for Ectodermal Dysplasia) but might have one of the less common forms of ED.

While this analysis provided a much larger and geographically diverse sampling than those conducted by the investigators included in the literature review, this research also was limited by selection bias in that all patients voluntarily completed the survey. Patients must opt-in to participate in the registry, and the data they submitted was not reviewed or validated by a clinician. In addition, not all patients completed all questions on the survey, so the actual sample sizes for the questions reviewed in this analysis varied from 81 – 164 for XLHED and 213 – 254 for all male HED respondents.

## Family History

Since XLHED is an inherited disorder, most of the respondents that completed the registry questions reported that multiple members of their family were also affected by the disease. 93% of XLHED respondents reported that at least one other family member was affected by an ectodermal dysplasia, and 58% reported two or more (n=137). This was very similar to the percentage reported by the broader male HED population – 92% of which reported at least one other family member affected by the disease, and 51% reported two or more (n=221). For a breakdown of responses, see Figure 7.

**Figure 7: NFED Registry – number of family members affected by Ectodermal Dysplasia**



Respondents to the NFED registry also indicated whether they were aware of any infant or childhood deaths by family members also suffering from an ectodermal dysplasia. 15% of XLHED respondents (n=136) and 12% of male HED respondents (n=219) indicated that they were aware of at least one infant or childhood death of family member suffering from an ectodermal dysplasia. Respondents with other forms of ectodermal dysplasia (excluding the HED disorders) reported a lower incidence of infant and childhood mortality – only 1% of these respondents reported an infant or childhood death in the family related to their disease (n=166). This research preliminarily indicates that XLHED has a higher rate of mortality than other forms of ED, but further research in this area needs to be conducted to more concretely understand current mortality rates and mortality trends of XLHED.

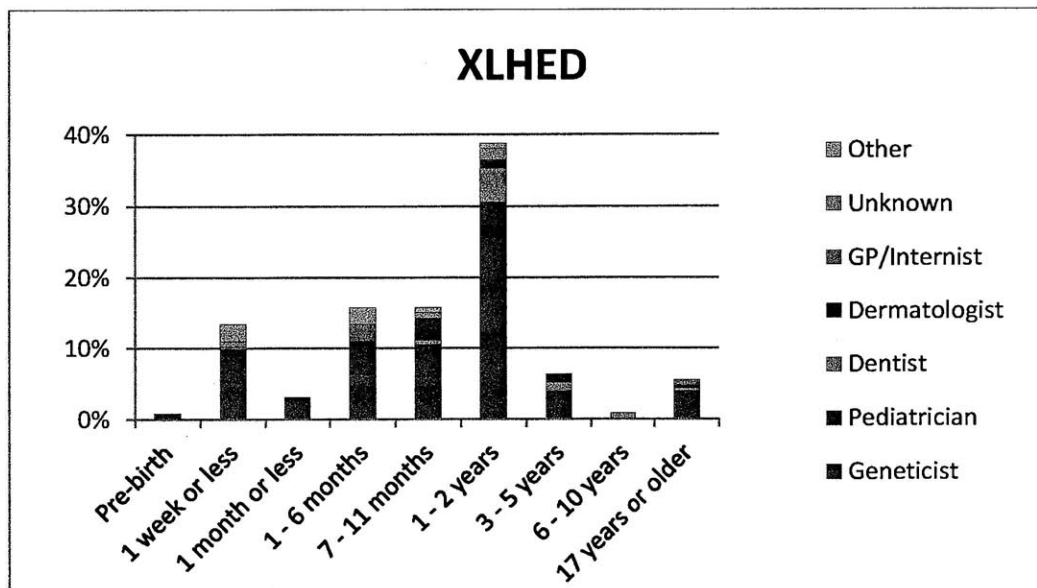
## Diagnosis

Half of the registry respondents reported that the diagnosis of XLHED was made by a geneticist (n=164). Other common respondents included pediatrician (17%), dentist (10%) and dermatologist (8%). Within the broader group of male HED respondents, 46% of diagnoses were made by a geneticist, 24% by a pediatrician, 10% by a dentist, and 8% by a dermatologist (n=264). In addition, 42% of XLHED

respondents (n=137) and 34% of male HED respondents (n=222) reported that the diagnosis was confirmed through genetic testing, which is required to make a confirmed diagnosis when genetic testing has not already occurred for other family members. Of the male HED respondents, 37% were unsure of their specific genotypic diagnosis (n=222).

The majority of respondents reported that a diagnosis was made within the first two years of life. 15% of XLHED respondents were diagnosed within or before the first week of life, 48% within the first year, and 87% within the first two years (n=136). Similarly, 15% of male HED respondents were diagnosed within or before the first week of life, 45% within the first year, and 84% within the first two years (n=220). The most common physician specialty to diagnose XLHED under the age is two years was a geneticist or pediatrician. The next most common physician specialties to diagnose during infancy were a dermatologist or general practitioner. Dentists generally are not involved in the diagnosis of XLHED until after one year of age, once tooth abnormalities become evident. For a breakdown of diagnosis by age and diagnosing specialist for XLHED respondents, see Figure 8.

**Figure 8: NFED Registry – age of diagnosis and diagnosing specialist for XLHED respondents**



The majority of non-HED respondents also reported diagnosis by a geneticist (59%; n=169), but also a higher diagnosis rate by dermatologists (19%) and lower for pediatricians (9%) and dentists (7%). This is likely due to the different ectodermal features affected by patients with those disorder. Other forms of ectodermal dysplasia also tended to be diagnosed later in life, with 37% of respondents reporting diagnosis after the age of 2, and 12% after the age of 17 (n=165).

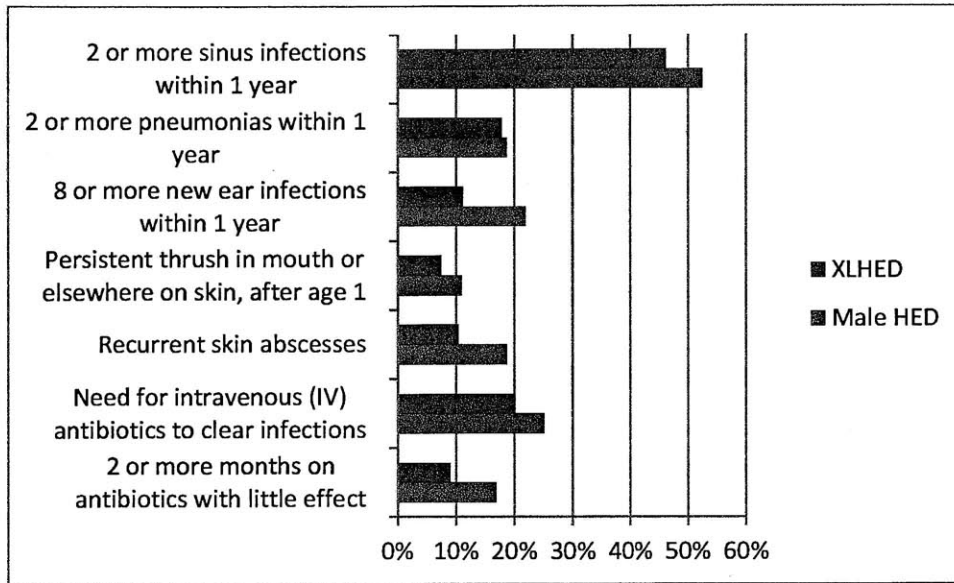
## General Health

As described previously, because they lack sweat glands, XLHED patients are unable to control their body temperature and often suffer from frequent fevers. 32% of XLHED (n=130) and 36% of male HED respondents (n=213) report requiring hospitalization for fevers, and 10% of XLHED (n=133) and 11% of male HED (n=218) respondents reported seizures related to heat intolerance. In addition, 55% of XLHED (n=142) and 58% of male HED respondents (n=232) reported restricted activity due to heat intolerance, and 23% of XLHED and 25% of male HED respondents reported frequent fevers.

As mentioned earlier, the ectodysplasin A protein is part of the NF $\kappa$ B transcription pathway, which is involved in inflammation and immune responses. As a result, some HED patients may experience immune deficiencies due to a genetic mutation in this pathway. In the NFED registry, 9% of XLHED (n=133) and 13% of male HED respondents (n=217) reported that a health professional had informed him that he had an immune deficiency.

HED patients also suffer from recurrent infections, due to their inability to produce adequate mucus. 46% of XLHED (n=134) and 53% of male HED respondents reported suffering two or more sinus infections within a year, 18% of XLHED and 19% of male HED respondents reported two or more pneumonias within one year, and 11% of XLHED and 22% of male HED respondents reported eight or more ear infections within a year. Further, 10% of XLHED and 19% of male HED respondents reported recurrent skin abscesses, and 7% of XLHED and 11% of male HED respondents reported experiencing persistent thrush in the mouth or on the skin. Members of both groups of patients also indicated difficulties in clearing these infections, with 20% of XLHED and 25% of male HED respondents requiring IV antibiotics to clear infections, and 9% of XLHED and 17% of male HED respondents reporting they were antibiotics for two or more months with little effect. See Figure 9 for a summary of infection responses for both the XLHED and broader male HED respondent groups.

**Figure 9: NFED Registry – infection history**



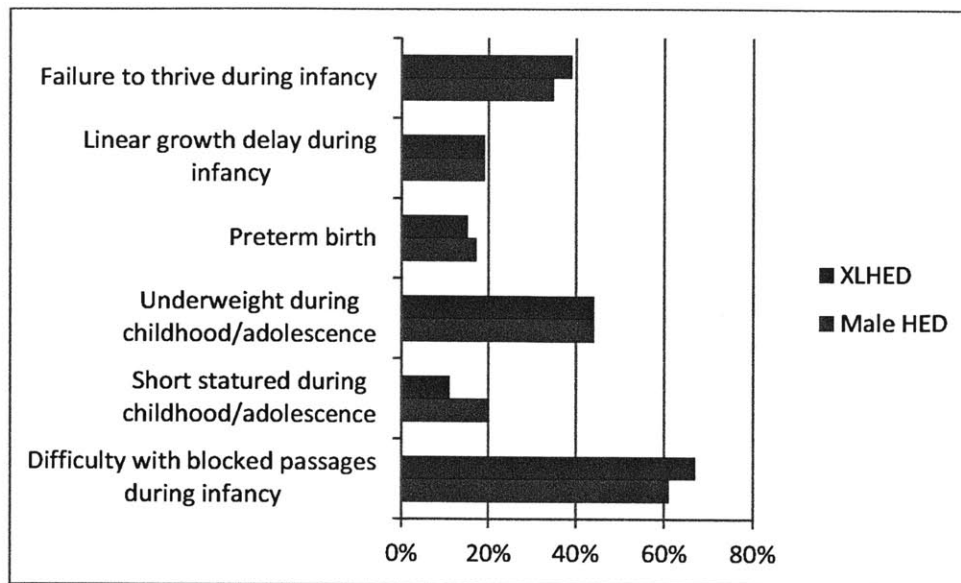
## Growth & Development

Concurring with findings from the literature review, male HED respondents reported being underweight in infancy and/or childhood, although on average being of normal stature and height. 39% of XLHED (n=134) and 35% of male HED respondents (n=219) reported failure to thrive as an infant (compared to a 5% rate in the general US population)<sup>19</sup>, and 44% of XLHED (n=132) and 44% of male HED (n=217) respondents reported being underweight as an adolescent. However, less than 20% reported linear growth delay as an infant or being short stature in adolescence. Further, 15% of XLHED (n=135) and 17% of male HED (n=220) respondents reported a preterm birth (compared to a 12% rate in the general US population).<sup>20</sup>

HED patients are also known to have feeding problems, in part due to nasal crusts that block their nasal passages. In the NFED registry, 67% of XLHED (n=133) and 61% of male HED respondents (n=216) reported difficulty with blocked nasal passages that interfered with feeding. See Figure 10 for a summary of growth and development for XLHED and male HED respondents.



**Figure 10: NFED Registry – growth & development**



Non-HED respondents reported a higher rate of preterm births (23%; n=165), but similar responses in height and weight through infancy and adolescence. However, many fewer respondents (17%; n=164) reported blocked nasal passages that interfered with feeding.

### **Limb/Finger/Toe Health**

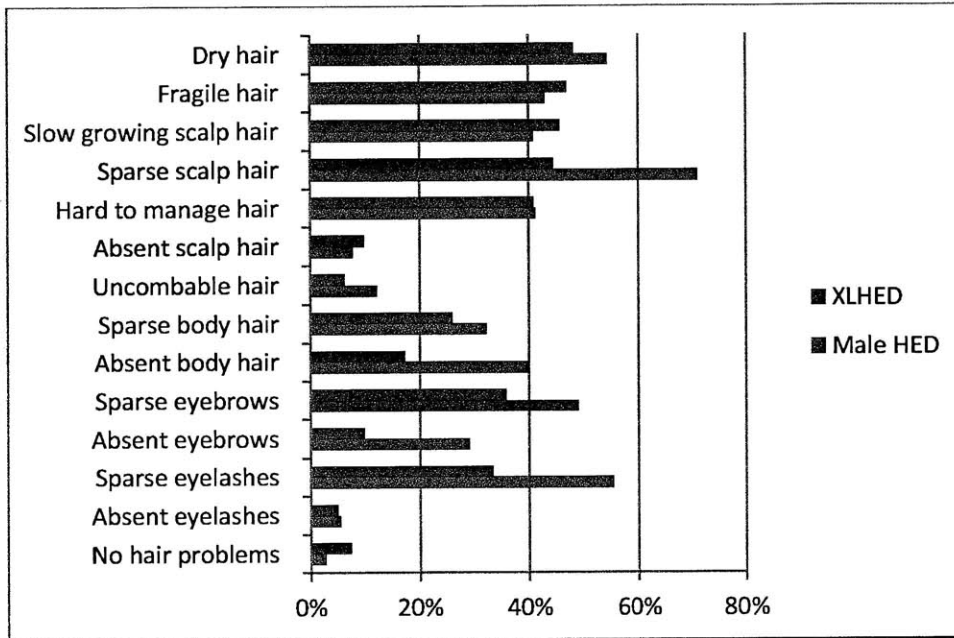
Abnormalities in the limbs, fingers, or toes were rarely reported by XLHED or male HED respondents – less than 2% of XLHED (n=122) and male HED (n=203) respondents reported such an issue. However, 52% of non-HED respondents reported an issue with their fingers (i.e. small, missing, fused, or split), and 52% reported an issue with their toes (n=164). These are clearly a common feature of other forms of ectodermal dysplasia, and presence of toe or finger abnormalities could be possible exclusion criteria when distinguishing HED patients from patients with other types of ED.

### **Hair/Skin/Nail Health**

One of the classic features of HED is sparse or thin scalp and body hair. 95% of XLHED (n=135) and 93% of male HED (n=245) patients report abnormal scalp hair. The most common problems reported include dry, slow growing, fragile, and sparse hair. Additionally, 67% of XLHED and 62% of male HED patients report either absent or sparse body hair, and 81% of XLHED 76% of male HED reported sparse or absent

eyelashes or eyebrows. Only 2% of XLHED and 3% of male HED respondents indicated no hair issues at all. See Figure 11 for a summary of responses related to scalp and body hair.

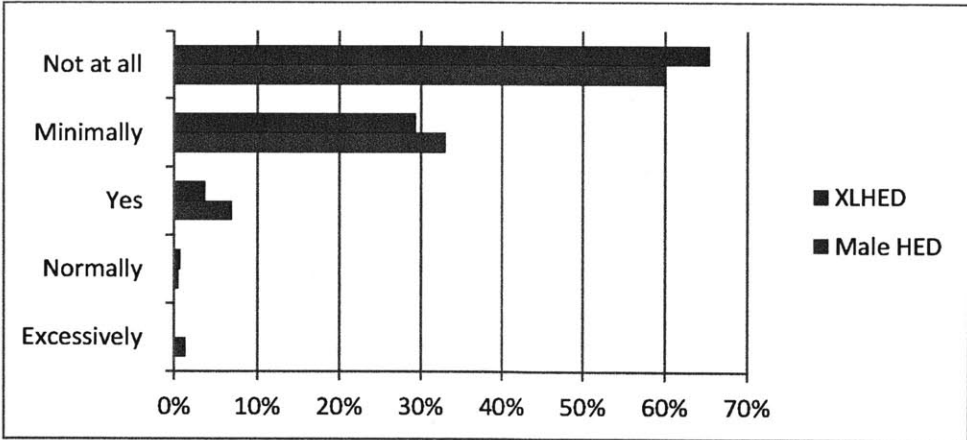
**Figure 11: NFED Registry – scalp and body hair**



Lack of hair does seem to be a common problem among patients suffering from other forms of Ectodermal Dysplasia. Similar percentages of patients reported problems with sparse or absent scalp and body hair. Therefore, lack of hair is not a distinguishing feature between HED and EDs.

As mentioned previously, another classic feature of HED is a reduced number or lack of sweat glands, impacting the ability of HED patients to sweat and increasing the risk of fevers and seizures due to high body temperatures. The data from the NFED registry supports this finding. 65% of XLHED (n=133) and 60% of male HED respondents (n=218) report being unable to sweat at all. An additional 29% of XLHED and 33% of male HED respondents report minimal sweating. And 10% of XLHED and male HED respondents reported seizures related to their inability to sweat. Those who are able to sweat report the most common locations to be the feet and hands. See Figure 12 for a summary of responses related to sweat frequency.

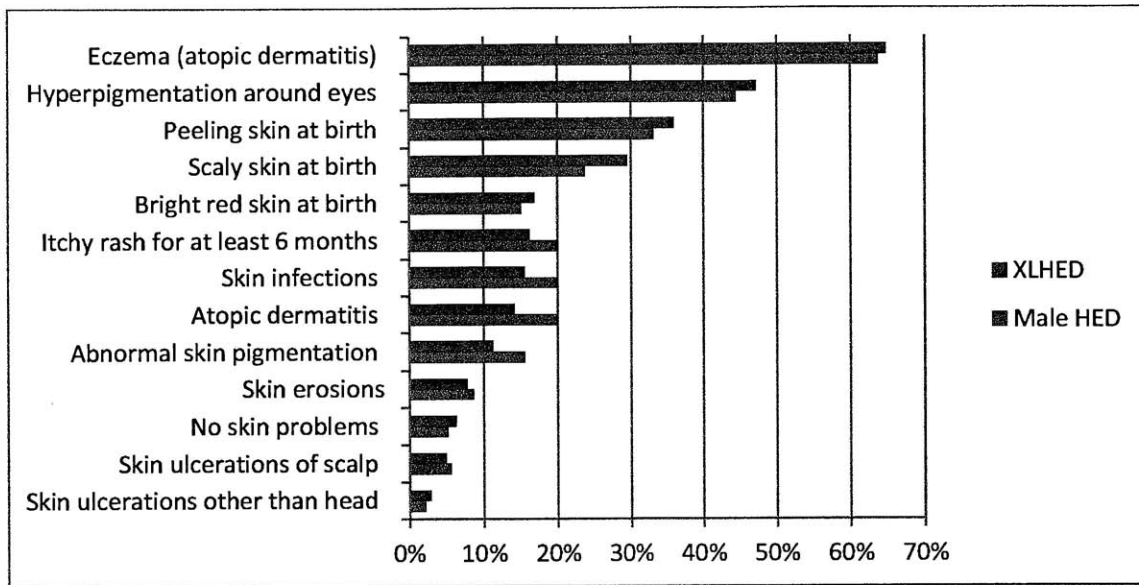
**Figure 12: NFED Registry – sweat frequency**



Respondents with another form of ED reported much less problems with sweating ability. 90% (n=162) reported some ability to sweat, with 12% reporting sweating excessively, 42% reporting minimal sweating capability, and 46% reporting normal sweating capability. Therefore, while a few of the other ED syndromes may affect sweating ability, the complete absence of sweat glands is a strong indicator that a patient suffers from a hypohidrotic ectodermal dysplasia, in conjunction with other criteria.

Most HED respondents reported skin issues – only 6% of XLHED (n=142) and 5% of male HED respondents (n=232) indicated they had experienced no skin problems at all. The most commonly reported problems were eczema (65% of XLHED and 64% of male HED), hyperpigmentation around the eyes (47% of XLHED and 44% of male HED), and peeling skin at birth (36% of XLHED and 33% of male HED). See Figure 13 for a full summary of reported skin issues.

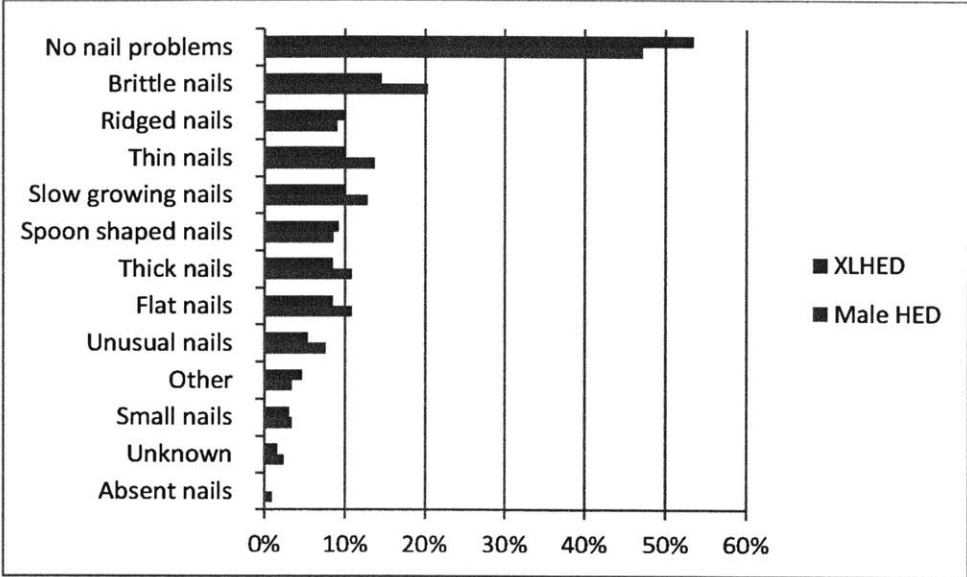
**Figure 13: NFED Registry – skin issues**



Non-HED ED patients also reported many of the skin conditions common to HED, including eczema (40%; n=72), abnormal pigmentation (28%), and red skin at birth (19%). These patients also experienced additional skin issues not reported by the male HED/XLHED population, including skin erosions (16%), and skin ulcerations of the scalp (12%) and outside the head (8%). Therefore, while useful to identifying potential patients with HED or XLHED, skin conditions alone cannot distinguish a patient with HED from another form of ED.

Nearly half of the male HED and XLHED patients reported no nail issues at all (n=212 and 352, respectively). The most commonly reported issues among these two patient groups were brittle, thin, ridged, or slow growing nails. See Figure 14 for a full breakdown of reported nail health issues for XLHED and male HED patients.

**Figure 14: NFED Registry – nail health**

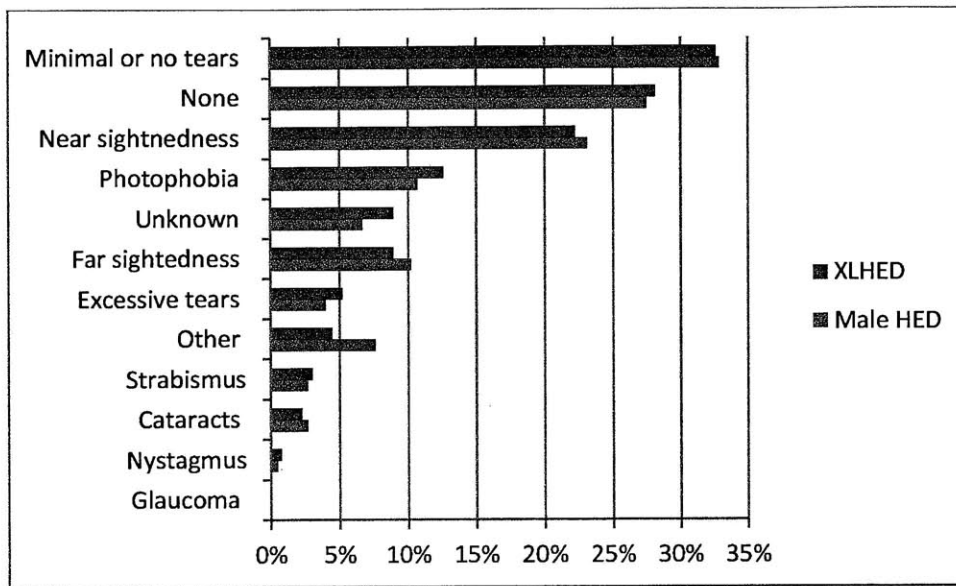


On the other hand, nail issues were much more commonly reported by patients who suffered from a other EDs. Only 7% (n=174) of these patients reported no nail issues. The most commonly reported nail problems included brittle nails (54%), unusual nails (51%), slow growing nails (48%), and ridged nails (44%). Given these differences, the presence of nail issues, in conjunction with other factors, could be a possible exclusion criterion when identifying HED patients from patients with other forms of ED.

**Eye/Vision Health**

Since XLHED patients are missing mucous glands, they have decreased levels of bodily fluids, including saliva and tears. The lack of tears was noted in the registry survey, as 32% of XLHED (n=131) and 30% of male HED (n=213) respondents reported being diagnosed with dry eyes. The most common products these patients reported using to combat dry eye include lubricating ointments or artificial tears products, such as Refresh, Refresh Plus, and Systane. A full breakdown of eye health issues is listed in Figure 15.

**Figure 15: NFED Registry – eye/vision health**

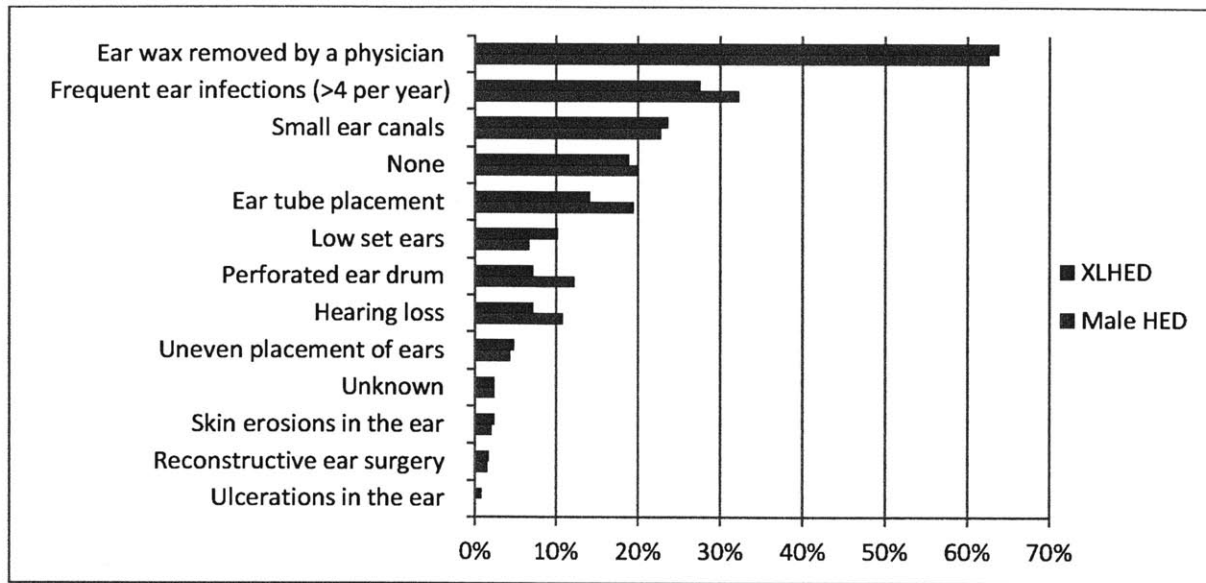


Patients that had been diagnosed with other EDs experienced less frequently reported issues with dry eyes, while some patients even reported excessive tears. Therefore, the ability of a patient’s eye to keep well-lubricated could be an exclusion criteria distinguishing HED from other forms of ED. In addition, 20% of non-HED ED patients (n=136) reported having corneal abrasions, over half of which were considered moderate to severe. The presence of corneal abrasions in male HED and XLHED was much more rare (7%), and reports of severity of reported abrasions were much more moderate (<20% moderate to severe) than those experienced by patients with other EDs.

### **Ear/Nose/Throat Health**

XLHED and male XED patients reported issues with frequent ear infections and wax build-up. 28% of XLHED (n=127) and 32% of male HED patients (n=211) reported experiencing at least four ear infections in one year. The issue with wax build-up could be related to the high number infections, as 64% of XLHED and 63% of all male HED patients report having to have had their ear wax removed by a physician. For a full breakdown of ear issues, see Figure 16.

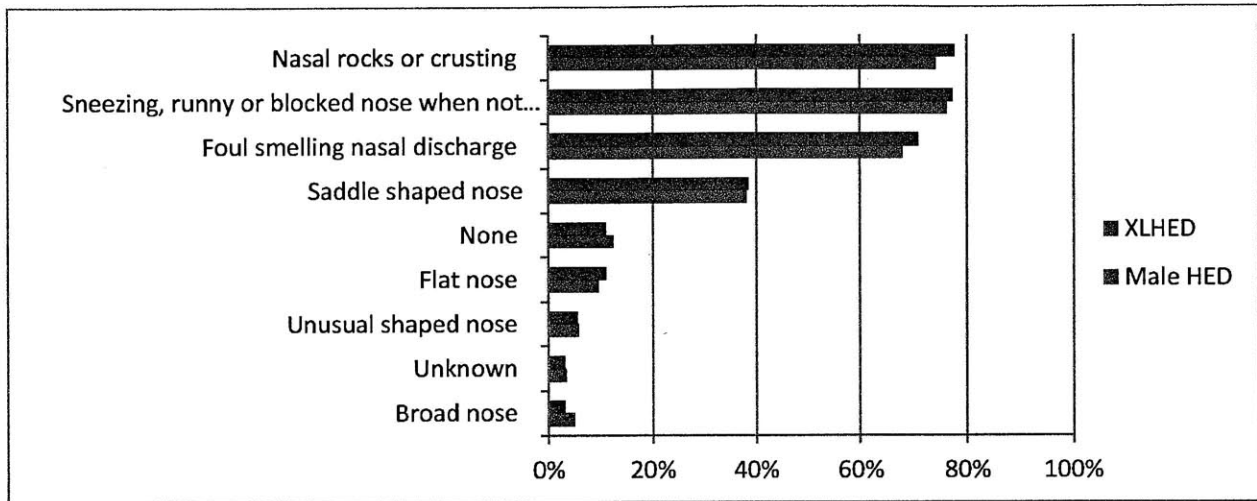
**Figure 16: NFED Registry – ear health**



While non-HED ED patients are also at similar risk for ear infections and ear wax build-up, they also reported a higher occurrence of ear tube placements – 49% of these patients (n=156) reported having an ear tube placed, as compared to 14% for HED. In addition, non-HED ED patients are more likely to have hearing loss and require the assistance of a hearing aid – 15% of non-HED ED patients report the use of a hearing aid, compared to <1% of male HED patients. The presence of ear tubes or the use of a hearing aid could be potential exclusion criteria to distinguish patients with HED from other forms of ED.

Patients with HED also tend to have characteristic nasal issues. One of the common features of XLHED noted in the literature review was a saddle-shaped nose. This observation was validated in the NFED registry analysis – 38% of XLHED (n=130) and male HED respondents (n=212) reported a saddle shaped nose, while an additional 15-20% reported either a broad, flat, or otherwise unusually appearing nose. In addition, 78% of XLHED and 74% of male HED patients reported nasal rocks or crusting, and 71% of XLHED and 58% of male HED report foul smelling nasal discharge. Most male HED patients combat these issues with the use of a humidifier (53%), saline flushes (77%), or using a bulb syringe or suction machine (38%). Finally, 77% of XLHED (n=132) 76% of male HED (n=210) patients report having trouble with sneezing, runny, or blocked nasal passages at a time when they were not suffering from a cold. For a summary of nasal health issues, see Figure 17.

**Figure 17: NFED Registry – nasal health**

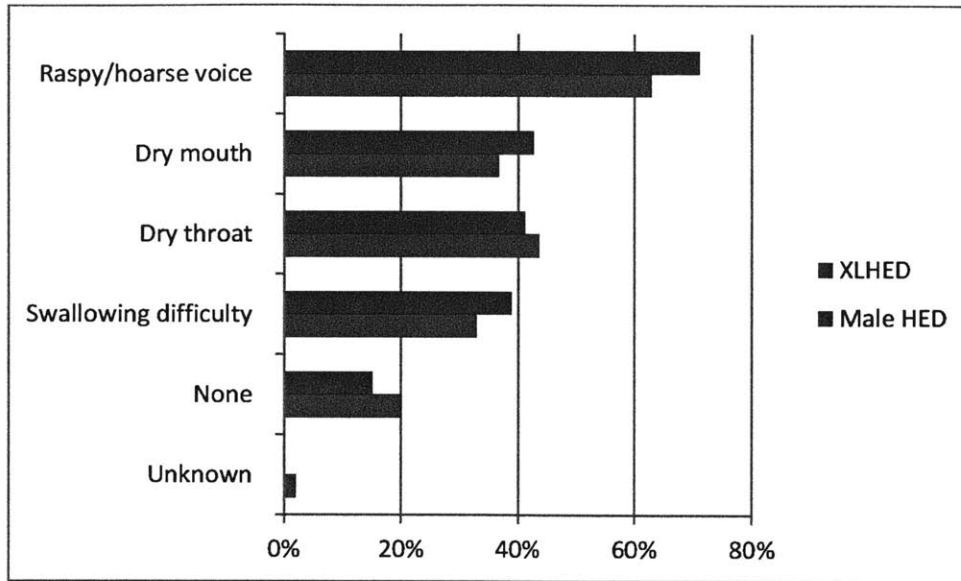


A higher proportion of patients with other EDs reported no nose health issues (46%; n=147), with the most common problems being nasal congestion without a cold (53%) and nasal rocks or crusting (29%). However, there is not a significant enough difference in these percentages to include nasal health criteria as an exclusion criteria for other forms of ED.

Similar to the lack of tears, many HED patients report decreased levels of saliva, causing dry mouth, difficulty swallowing, and a raspy/hoarse voice. These symptoms are also prevalent, though in less frequency, in patients with other forms of ED, and therefore would not be strong candidates for exclusion criteria in an identification algorithm. A breakdown of reported throat issues for male HED and XLHED patients is presented in Figure 18.



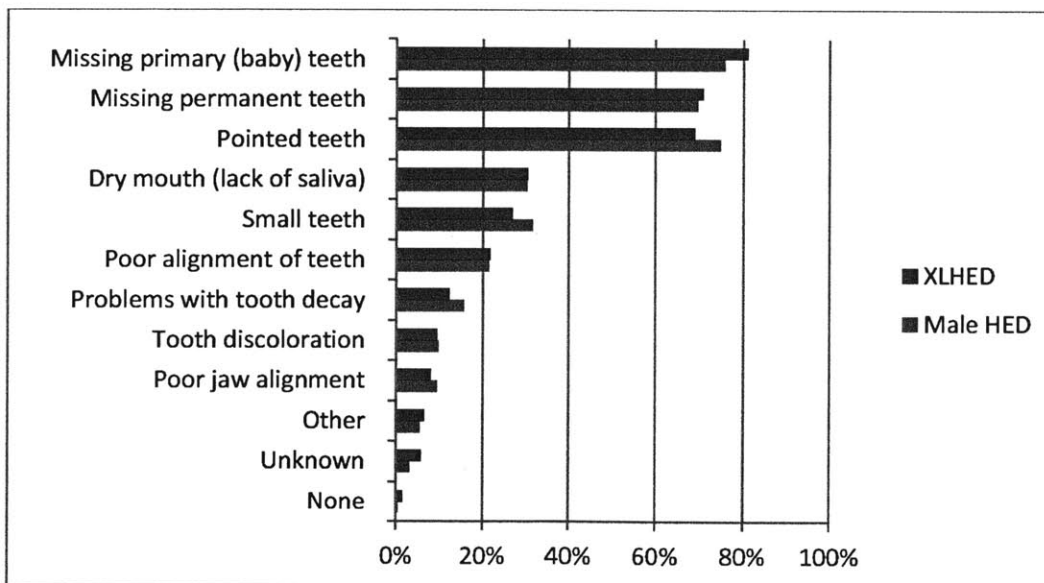
**Figure 18: NFED Registry – throat health**



## Oral/Dental Health

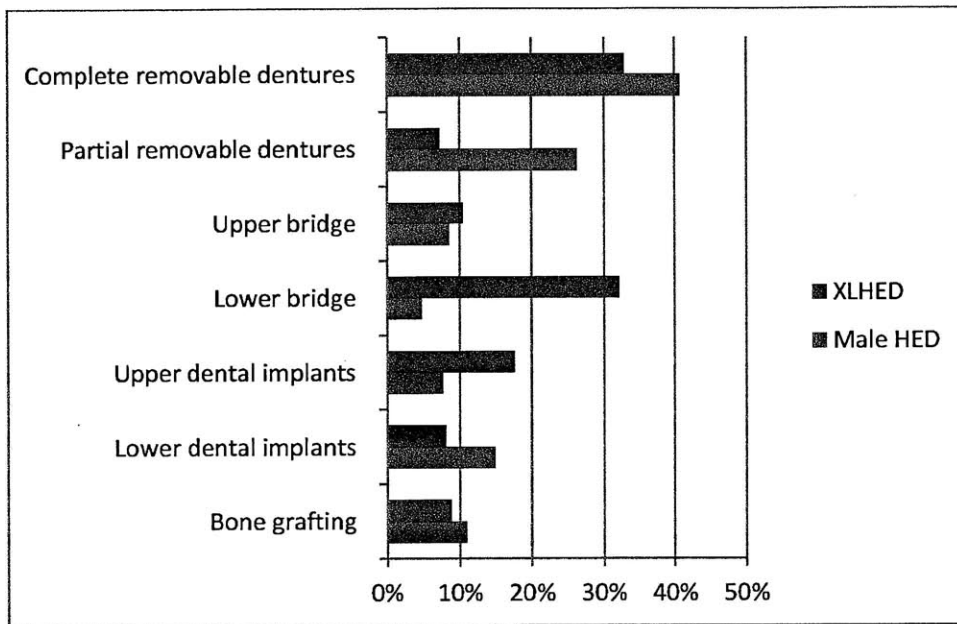
One of the key features of HED is the presence of missing or oddly-shaped teeth. Over 70% of male HED (n = 224) and XLHED (n=138) reported missing primary and permanent teeth. Over 70% of the teeth that they did have were pointed, approximately 30% were small, and 20% were poorly aligned. For a full breakdown of oral health issues, see Figure 19.

**Figure 19: NFED Registry – oral health**



In order to manage the dental issues, most male HED patients choose to undergo some form of dental treatment or surgery. Treatment options could include a bridge, dental implants, bone grafting, and dentures. Of the patients surveyed in the NFED registry, about 70% reported either utilizing complete or partially removable dentures, while most of the remaining reported utilizing bridges or dental implants. Of those who wear dentures, most begin at the age of 2-4 years, while dental implants are more commonly placed only on the lower jaw and after the age of 17. For a breakdown of reported dental treatment procedures, see Figure 20.

**Figure 20: NFED Registry – dental treatments**



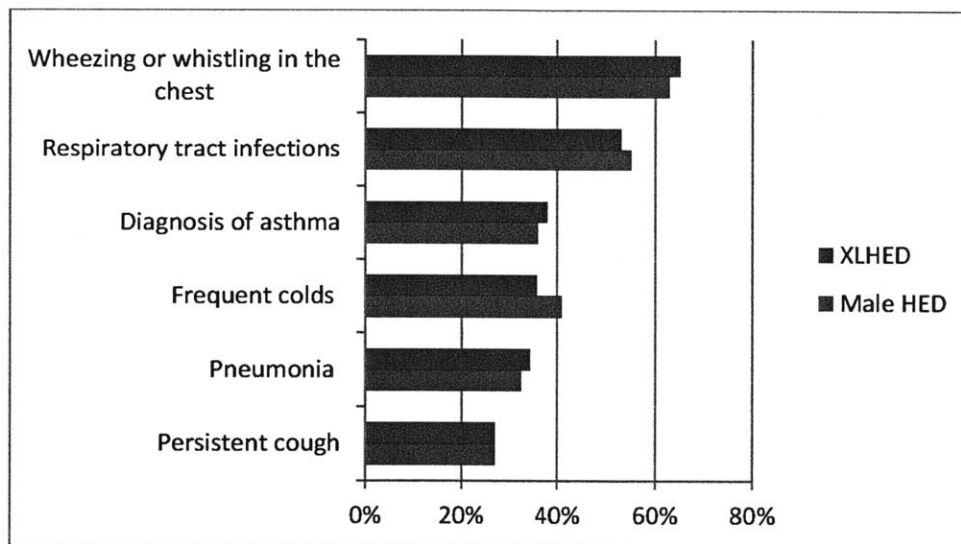
Additionally, HED patients may require jaw surgery and/or braces in order to correct teeth misalignment. 20% of XLHED (n=102) and 23% of male HED (n=180) reported requiring braces or other orthodontic treatments. 19% of XLHED (n=105) and 24% of male HED (n=181) have required tooth extractions as part of their dental treatment plan. Finally, 20% of XLHED (n=105) and 15% of male HED (n=176) have required jaw surgery, including surgery required to place dental implants.

While non-HED ED patients reported oral/dental issues as well, this group of patients more commonly reported abnormal teeth (small or pointed, abnormal alignment) than complete tooth loss. Over a third of the non-HED ED patients also reported having a cleft lip or palate, most of which have since had surgically repaired. The presence of a cleft palate or surgery to repair the palate could be a clear indicator that an ED patient has a form of ED other than HED.

## Respiratory

Patients suffering from HED often experience increased respiratory infections due to decreased mucus production and immune system dysfunction. Nearly half of the patients surveyed reported frequent colds, pneumonias, or respiratory tract infections. Over half reported wheezing or whistling in the chest. Nearly a third also reported a prior diagnosis of asthma. While these symptoms are present in other non-HED forms of ED, the prevalence of these issues is significantly higher for patients suffering from XLHED or one of the other forms of HED. For frequency of respiratory issues, see Figure 21.

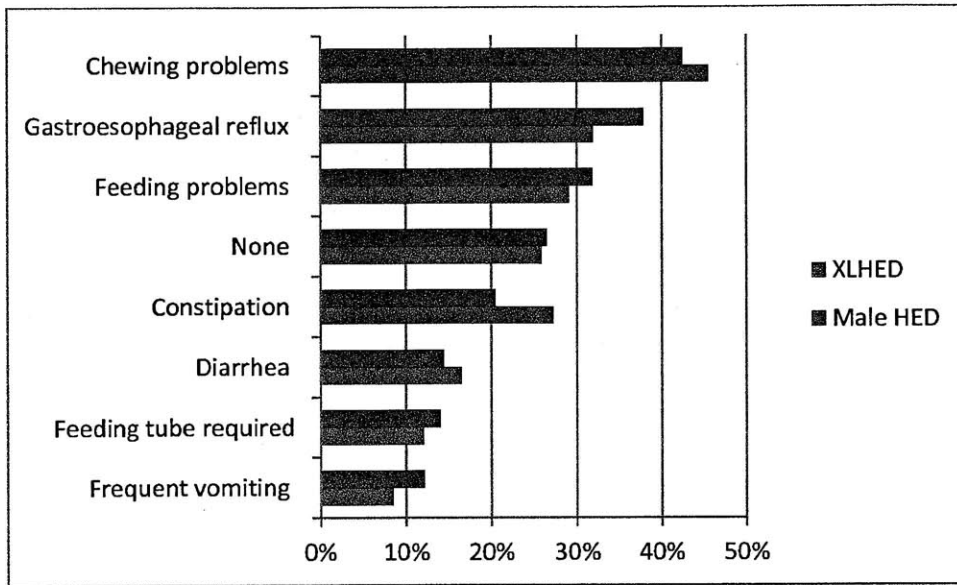
**Figure 21: NFED Registry – respiratory issues**



## Digestive System

Children affected with HED tend to have problems chewing and feeding, largely due to missing or abnormal teeth. In addition, due to their reduced production of body fluids, including mucous in the colon, they also tend to report issues with constipation and gastroesophageal reflux. These symptoms are of similar prevalence in patients with other forms of ED, and therefore while distinguishing among ED patients, could not be used as inclusion criteria to identify HED patients with an ED population. For a full breakout of digestive health issues for HED patients, see Figure 22.

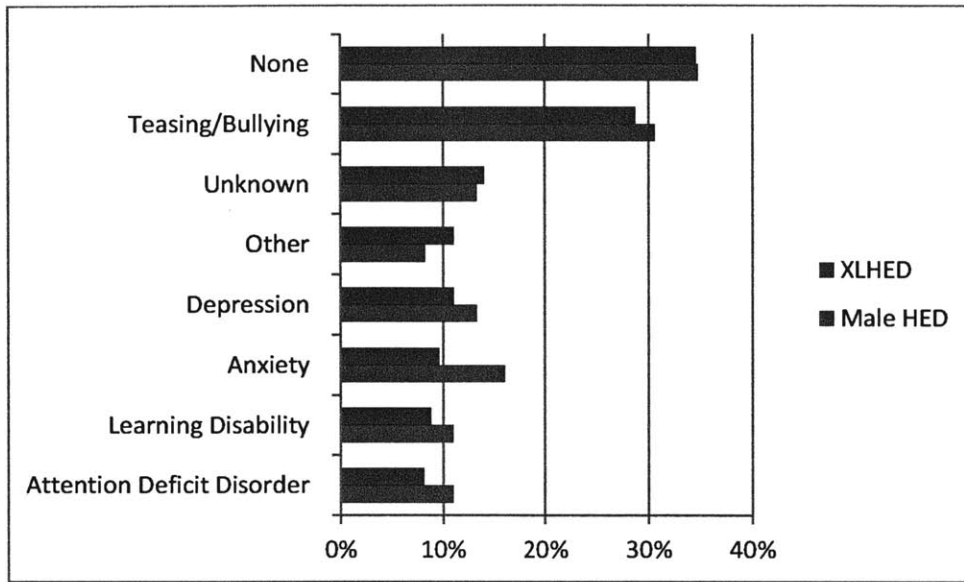
**Figure 22: NFED Registry – digestive health**



## Quality of Life

As also mentioned during the literature review, HED patients do suffer some quality of life issues, primarily psycho-social issues related to teasing from peers about their appearance. The impact of the disease on academic success as a child generally starts during elementary school and tends to lessen with age: 15% of HED patients report their disease affecting elementary school success, 11% in middle school, and 7% in high school, and 3% in college (n=210). 14% of respondents reported that their disease limits their ability to work, likely due to their inability to cool their body in hot temperatures. A listing of reported quality of life issues for XLHED and male HED patients is presented in Figure 23.

**Figure 23: NFED Registry – quality of life health**



## Summary

A summary of potential inclusion and exclusion criteria that could be incorporated into an identification algorithm, based on the results of the registry analysis, are presented in Table 2 below.

**Table 2: NFED Registry – summary of potential inclusion and exclusion criteria**

Category	Inclusion Criteria	Exclusion Criteria
<b>General Health</b>		
	Heat intolerance / fevers	
	Recurrent infections	
<b>Growth &amp; Development</b>		
	Underweight / low BMI	
	Failure to thrive / feeding issues	
<b>Limb / Finger / Toe Health</b>		Abnormal fingers or toes
<b>Hair / Skin / Nail Health</b>		
	Thin scalp / body hair	
	Reduced sweat glands	Presence of sweat glands
	Eczema	
	Hyperpigmentation of the eyes	
	Peeling skin	
		Skin erosions
		Ulcerations of the scalp
		Abnormal nails
<b>Eye / Vision Health</b>		
	Dry eyes	Excessive tears
		Severe corneal abrasions

<b>Ear/Nose/Throat Health</b>	
	Frequent ear infections
	Ear wax build-up
	Saddle-shaped nose
	Nasal rocks / crusting
	Foul smelling nasal discharge
	Blocked nasal passages
	Dry mouth / lack of saliva
	Ear tube placements
	Use of hearing aid
<b>Oral / Dental Health</b>	
	Missing / abnormal teeth
	Use of dental implant / dentures
	Prior jaw surgery
	Cleft lip / palate
<b>Respiratory</b>	
	Frequent respiratory infections
	Asthma
<b>Digestive System</b>	
	Constipation
	Gastrointestinal reflux
<b>Quality of Life</b>	
	Anxiety
	Depression
	Attention deficit disorder

## Electronic Medical Record Review

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### Methodology

Several academic medical centers in the Boston area offer data repositories for researchers studying medical questions. The Brigham and Women's Hospital utilizes a data warehouse called RPDR (Research Patient Data Registry), and the Children's Hospital of Boston maintains its i2b2 database (informatics for integrating biology at the bedside). Between these two systems, millions of patients records and claims data are documented and available for research pending the approval of each institution's respective Internal Review Board (IRB).

While EMR databases often require approval to access for research, they allow the researcher to review detailed, patient-level medical records. On the other hand, datasets from traditional, claims databases can typically be purchased without approval from an IRB, and patient-level detail can be analyzed once a

Data Use Agreement is in place, only diagnosis codes and procedural codes are available for analysis. However, utilizing the RPDR or i2b2 system, an investigator has the ability both to analyze how a patient was coded for billing purposes and to review a patient's full medical record as needed to validate diagnoses and provide a detailed clinical history.

My objectives in working with the EMR databases were two-fold – first, I planned to analyze the charts of patients with a diagnosis code of Ectodermal Dysplasia as a way to supplement the literature review and registry analysis in my understanding of the symptoms and diagnoses of HED. Second, I intended to utilize the claims data within these databases to build an algorithm that would positively identify HED patients without falsely identifying any the non-HED control patients.

### ***Internal Review Board (IRB) Approval Process***

In order to gain access to these systems, I first had to seek approval by each institution's respective Internal Review Board (IRB). As an MIT student, I needed approval from MIT's IRB, known as COUHES. My study qualified for exempt status, since the research only involved the collection and study of existing documents and patient records, and the study presented minimal risk to the patients whose records I was reviewing. Therefore, I was awarded exempt review by COUHES.

After securing approval from MIT, I approached the Partners and Children's Hospital IRBs to initiate the approval process. For the Partners IRB application, I worked with Dr. Sebastian Schneeweiss and Kelly O'Keefe at the Division of Pharmacoepidemiology at the Brigham and Women's Hospital. The protocol was submitted on January 1, 2011, and I received feedback from the IRB on January 27, 2011. I had initially included Dr. Kenneth Huttner as part of the research team, who has an appointment as a clinician at MGH. His involvement in the study would have allowed us to use records from both the MGH and Brigham & Women's Hospital, increasing the number of patients we would be able to analyze as well as improving the comprehensiveness of each patient's medical record. However, the Partners IRB would not approve the protocol with Dr. Huttner listed as an investigator, due to a conflict of interest with his employment at Edimer Pharmaceuticals. I revised the protocol and resubmitted my responses and requested supplemental documentation on February 7<sup>th</sup>. On March 1<sup>st</sup>, I received a second response from the IRB requesting the same information I had provided on February 7<sup>th</sup>. I restructured my response into the requested format and resubmitted the same day. Finally, on March 7<sup>th</sup>, I received IRB approval to move forward on the project.

The IRB approval process at Children’s Hospital was handled by our primary investigator, Dr. Jonathan Bickel. We submitted our initial request on February 5<sup>th</sup>, received a response from the IRB on February 27<sup>th</sup>. We made the requested changes and submitted a conflict of interest form, but due to internal issues at the IRB, did not receive approval to move forward with the Children’s data until March 31<sup>st</sup>.

For both IRB applications, I provided a clear, step-by-step outline of what we planned to do during our study, and why the study posed minimal to no risk for study participants. The research methodology submitted to Partners’ IRB is re-printed in Appendix A.

### ***Patient Chart Review & Patient Identification***

In order to develop an identification algorithm for patients with Hypohidrotic Ectodermal Dysplasia, I needed to identify a group of patients with a confirmed HED diagnosis from which to develop inclusion criteria. Since there are no ICD-9 diagnosis codes for HED, I started by filtering each database to include only persons with a male gender and an ICD-9 diagnosis code of 757.31 for Ectodermal Dysplasia.

To determine whether a patient with an ICD-9 diagnosis of Ectodermal Dysplasia could be confirmed for a clinical diagnosis of HED, I worked with the primary investigator at each site to perform a chart review. I performed the chart review under the guidance of Dr. Sebastian Schneeweiss at the Brigham and Women’s Hospital, and Dr. Jonathan Bickel performed the chart review at Children’s Hospital of Boston. If a clear diagnosis of HED was present in the clinical notes, or a confirming genetic test provided evidence of HED, the patient was included in our HED cohort. For those without a clear clinical diagnosis, the patient’s record must show evidence that the patient exhibited all three of the hallmark HED features (reduced sweating, reduced teeth, sparse/absent hair) in order to be included in the HED cohort. For those that exhibited only one or two of the hallmark features, we sought confirmation from HED expert, Dr. Ken Huttner. For all other uncertain cases, we excluded the patient record from the analysis. The form we used to track confirmed and possible HED diagnoses is included in Appendix B.

We then pulled a second dataset from each database of non-ED male patients who could be used as a control for an identification algorithm. The control data would allow us to test potential algorithms, and develop statistical measures of each algorithm’s accuracy.



## Children's Hospital of Boston

An initial query of the i2b2 database at Children's Hospital of Boston showed a total of 131 patients coded with the ICD-9 757.31 for Ectodermal Dysplasia, of which 67 were male and potential candidates for our analysis.

Nine of the 67 were historical patients whose claims data been uploaded into i2b2 but had no associated electronic medical record data. Since we were unable to confirm a diagnosis of HED for these patients using EMR data, and the claims data alone could not support a decisive diagnosis, these nine were filtered out of the analysis.

An additional thirteen patients had diagnoses present in their EMR other than Hypohidrotic Ectodermal Dysplasia. The diagnoses include:

- Autoimmune Polyendocrinopathy Candidiasis Ectodermal Dystrophy (APECED) or Whitaker Syndrome – an immune deficiency disorder characterized by persistent yeast infections, dysfunction of the parathyroid and adrenal glands; causing hypocalcaemia, hypoglycemia, hypotension, and severe reactions to infection<sup>21</sup>
- Chondroectodermal Dysplasia (Ellis-van Creveld Syndrome) – genetic disorder of the skeletal system, causing anomalies such as polydactyl, atrial septal and other congenital heart defects, abnormal fingernails, dwarfism, and cleft palate<sup>22</sup>
- Delleman's Syndrome (Oculocerebrocutaneous Syndrome) – genetic disorder characterized by cysts in the skull that surround the eye; brain abnormalities that can cause mental retardation and/or seizures; and skin malformations, the most common being skin tags<sup>23</sup>
- Dyskeratosis Congenita (Zinsser-Engman-Cole Syndrome) – bone marrow failure disorder characterized by skin hyperpigmentation, abnormal nail development, and oral keratosis<sup>24</sup>
- Ectrodactyly–Ectodermal Dysplasia–Cleft Syndrome (EEC Syndrome) – autosomal recessive disorder characterized by split hand or foot malformations; abnormalities of the skin, hair or nails; and lip or cleft palate<sup>25</sup> [3 patients]
- Hidrotic Ectodermal Dysplasia (Clouston Syndrome) – disorder characterized by sparse hair, abnormal nails, hyperpigmented skin, and clubbing or fusing of the fingers<sup>26</sup> [2 patients]

- Marshall-Smith Syndrome – a malformation disorder characterized by accelerating bone aging, respiratory problems, unusual facial characteristics, and mental retardation<sup>27</sup>
- Osteogenesis Imperfecta – a genetic disorder characterized by brittle bones causing multiple bone fractures; early hearing loss; short stature; and blue sclera<sup>28</sup>
- Robinow Syndrome – a genetic disorder characterized by dwarfism; craniofacial abnormalities, skeletal malformations, and genital abnormalities<sup>29</sup>
- Witkop Tooth-Nail Syndrome – an autosomal dominant genetic disorder characterized by abnormal nails and toenails and hypodontia; however, unlike HED, hair and sweat function are normal<sup>30</sup>

While it is possible that one or more of the thirteen patients with a diagnosis above also suffers from HED, our primary investigator, Dr. Jonathan Bickel, was unable to confirm the HED diagnosis from the medical notes in any of these patients' medical records. Therefore, these thirteen were excluded from further analysis.

Two other patients were diagnosed with ectodermal dysplasia with immune deficiency. While a NEMO mutation could occur in conjunction with an EDA mutation (cause of HED), and there were several confirmed cases of HED with a NEMO mutation in this dataset, there was no mention of any of the cardinal features of HED in these two patients medical records (reduced sweating, missing/abnormal teeth, sparse hair), so they were excluded from further analysis.

Two other patients did not have a clear diagnosis present, but exhibited two of the cardinal features of HED. However, these two patients also had symptoms such as dystrophic nails and/or clubbing of the fingers. These features are not common for patients with HED, and are more likely linked to the other forms of ED. Therefore, they were excluded from further analysis.

Fifteen of the 67 patients had no record of any of the cardinal features of HED in their medical record. Two of these fifteen had also undergone genetic testing, with normal results. Therefore, since there was no data to support a diagnosis of HED, these fifteen were also excluded from further analysis.

Finally, three of the 67 patients had record of only one of the cardinal HED features. Two of the three were reported as having missing or abnormal teeth, and one was reported with abnormal sweating.

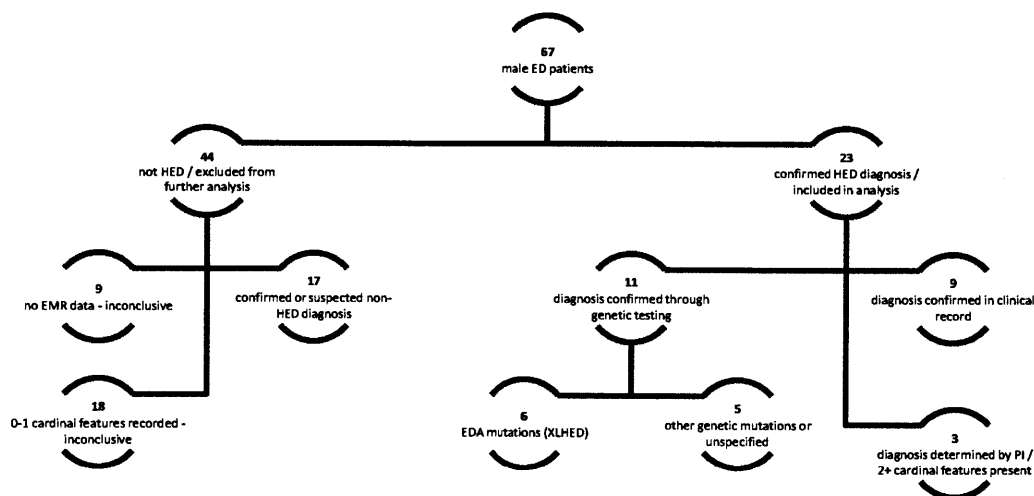
However, the information in their medical records and claims data was inconclusive to confirm a diagnosis of HED, and they were excluded from further analysis.

In the total, 23 patients were confirmed as having some form of Hypohidrotic Ectodermal Dysplasia by Dr. Bickel – either by a conclusive diagnosis included in the medical record, a genetic test confirming an EDA mutation, or a record of at least two of the cardinal features of the disease as well as multiple records of other common symptoms of HED (respiratory issues, chronic nasal drainage, dry/peeling skin, cranial deformity, etc).

- Eleven of the 23 patients’ diagnoses were confirmed through genetic testing. Of these, six had mutations in the EDA gene, one with a mutation in the EDAR gene, four in the NEMO or IKBG gene, and one was unspecified.
- Nine of the 23 patients had a clinical diagnosis of HED, but there was no mention in their medical record of confirmation by genetic testing.
- Three of the 23 patients were confirmed as having the disease by Dr. Bickel and Dr. Huttner. They had a record of at least two of the cardinal features of HED, and other notes in their record were also positively suggestive of an HED diagnosis. These patients were included in our analysis.

A summary of diagnoses of the 67 ED patients in the i2b2 database is presented in Figure 24.

**Figure 24: Summary of Diagnoses – Children’s Hospital of Boston**



## Brigham and Women's Hospital

The Brigham and Women's Hospital does not run a pediatric service, and since most diagnoses of HED are made during childhood or infancy, there were many fewer patients with a diagnosis code of Ectodermal Dysplasia. In total, there were 12 patients with an ICD-9 code of Ectodermal Dysplasia in the Brigham's RPDR database, and the medical record and claims data for these patients were limited.

Three of the ED patients had no medical record data. Therefore, an HED diagnosis could not be confirmed, and these patients were excluded from the remainder of our analysis.

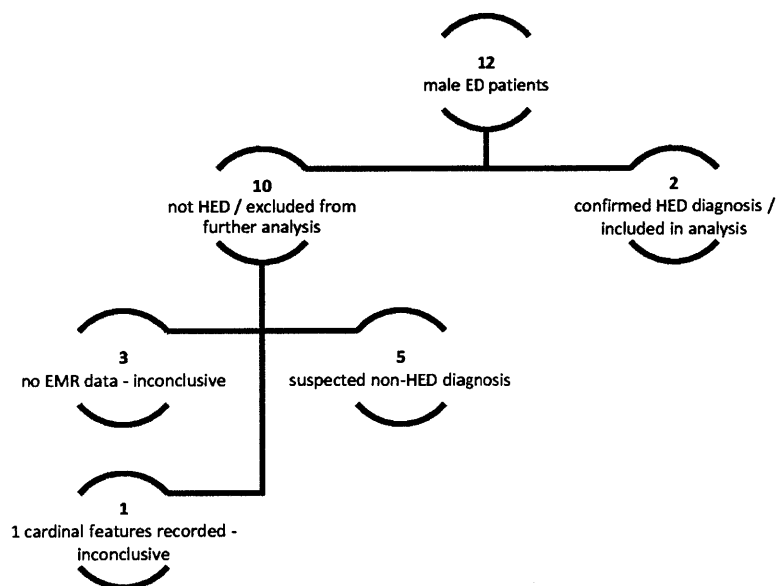
Six of the ED patients had no record of any of the hallmark features of HED. These six also had either had evidence of normal function of the skin, hair, or sweat glands; or they exhibited characteristics of another form of ED (i.e. dystrophic nails, abnormal fingers/toes, skin tags).

One patient exhibited one of the hallmark features of HED – dyshidrosis – but the remainder of their record did not contain enough supporting data to confirm an HED diagnosis. Therefore, this patient was excluded from further analysis.

In total, two patients from the Brigham dataset had a clinically confirmed diagnosis of HED, although neither diagnosis was confirmed through genetic testing.

A summary of diagnoses of the 12 ED patients in the RPDR database is presented in Figure 25.

**Figure 25: Summary of Diagnoses – Brigham & Women's Hospital**



# Claims Data Analysis

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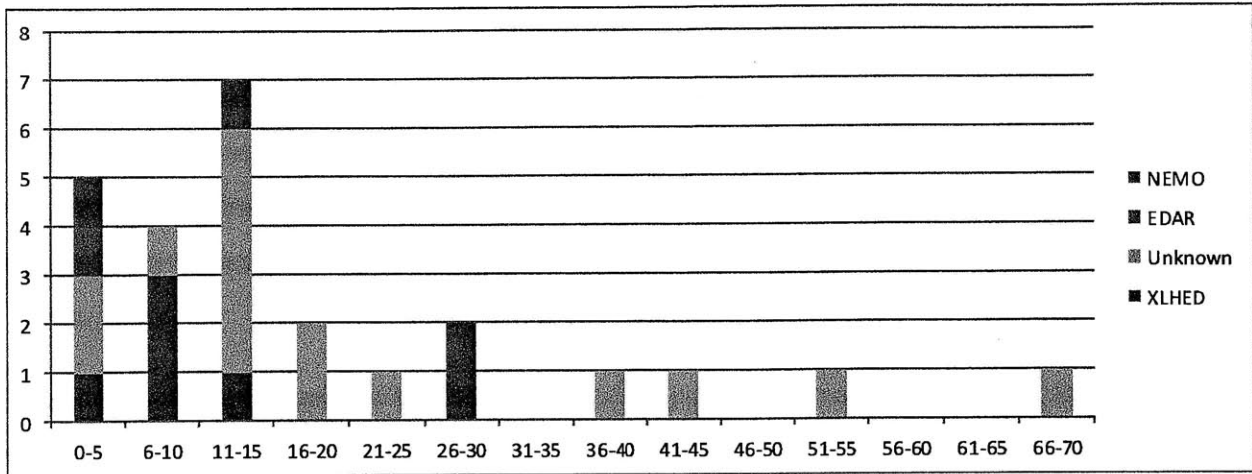
After confirming a diagnosis of HED using the electronic medical record, I next looked at the claims data for these patients to identify trends in diagnosis codes that could be used as inclusion criteria in an identification algorithm. Of the 23 confirmed patients in the i2b2 (Children's Hospital of Boston) database, 17 had associated claims data. Both diagnosis codes (ICD-9) and procedure codes (ICD-9, CPT-4) were available for these 17 patients; however, there were very few patients with procedure claims and there was little overlap in procedure codes, so I focused my analysis on the ICD-9 diagnosis codes. Both of the two confirmed patients in the RPDR (Brigham & Women's Hospital) database had claims data – only ICD-9 diagnosis codes were available for these patients.

The total number of HED patients with claims data was too small to be able to divide into a train and test population, which was initially planned in order to develop and validate an identification algorithm. Therefore, I instead analyzed descriptive statistics of the claims data in order to better understand how these patients flow through the healthcare system, and what identification criteria might be valuable for an investigator studying a larger patient population in the future.

## Patient Demographics

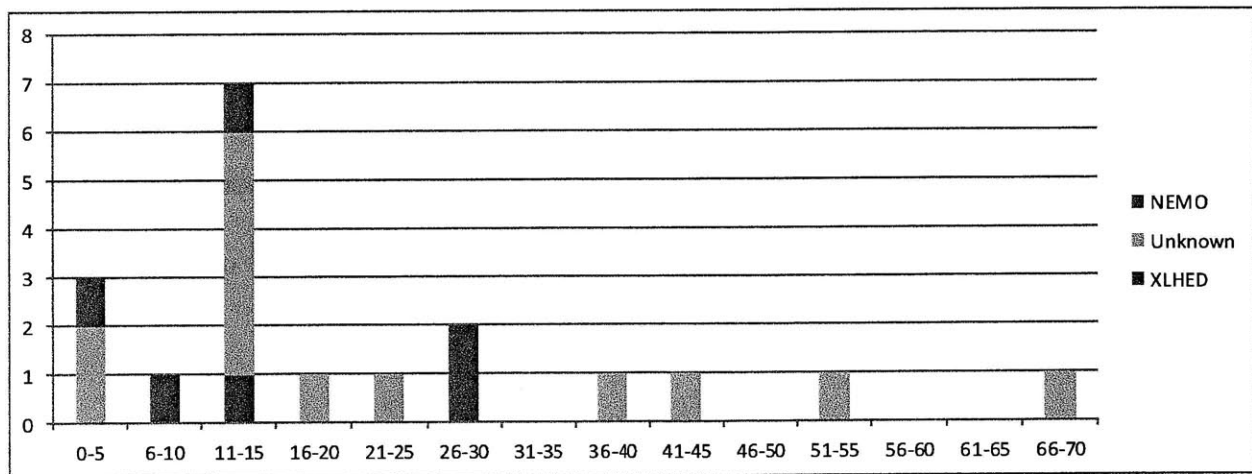
There were a total of 25 patients in the Children's Hospital of Boston and Brigham & Women's Hospital databases confirmed to have HED. Patient age varied from 2 to 70, with an average age of 18 and standard deviation of 17. A distribution of patient age by diagnosis (when known) is presented in Figure 26 below.

**Figure 26: HED Patient Distribution – by Age and Genetic Mutation**



There were a total of 19 HED patients with claims data. Patient age varied from 2 to 70, with an average age of 22 and standard deviation of 18. A distribution of patient age by diagnosis (when known) is presented in Figure 27 below.

**Figure 27: HED Patient Distribution – by Age and Genetic Mutation (Patients with Claims Data Only)**



### Diagnosis Codes (ICD-9)

The International Classification of Diseases, ninth edition (ICD-9) is a standardized series of codes to classify diagnoses and procedures. This system is managed by the National Center for Health Statistics and Centers for Medicare and Medicaid Services.

In order to analyze trends in diagnosis at a higher level than the detailed ICD-9 values, I first mapped of the claims data to three levels within the ICD-9 diagnosis hierarchy. The results of this high-level analysis are listed in Table 3 below, and a detailed analysis of diagnoses patterns within each category follows. A full list of ICD-9 diagnosis codes and their frequencies in the dataset are listed in Appendix C.

For the most common diagnosis categories, I studied the distribution of diagnosis codes within the category by patient. I noted those diagnoses in particular with a frequency of three or more patients (excluding the four with known NEMO mutations; the patient with an EDAR mutation did not have associated claims data) – both to confirm the presence of known symptoms of HED, as well as to identify any new trends in the disease presentation.

**Table 3: ICD-9 Diagnosis Codes Summary**

Codes	Category	Patient Count	Excluding NEMO
Patient Base		19	15
740-759	Congenital Anomalies	17	13
780-799	Symptoms, Signs, And Ill-Defined Conditions	13	9
460-519	Diseases Of The Respiratory System	12	8
680-709	Diseases Of The Skin And Subcutaneous Tissue	10	7
V01-V91	Supplementary Classification Of Factors Influencing Health Status And Contact With Health Services	10	6
520-579	Diseases Of The Digestive System	9	5
320-389	Diseases Of The Nervous System And Sense Organs	9	5
240-279	Endocrine, Nutritional And Metabolic Diseases, And Immunity Disorders	8	4
001-139	Infectious And Parasitic Diseases	7	3
580-629	Diseases Of The Genitourinary System	6	2
800-999	Injury And Poisoning	6	3
280-289	Diseases Of The Blood And Blood-Forming Organs	5	2
710-739	Diseases Of The Musculoskeletal System And Connective Tissue	5	2
290-319	Mental Disorders	5	4
E000-E999	Supplementary Classification Of External Causes Of Injury And Poisoning	5	2
390-459	Diseases Of The Circulatory System	4	1
140-239	Neoplasms	2	1
760-779	Certain Conditions Originating In The Perinatal Period	1	0

## Congenital Anomalies

Despite that it was the filtering criteria for these patients, only seventeen of the nineteen HED patients had an ICD-9 code for Congenital Ectodermal Dysplasia (757.31) in their claims history. The two patients from RPDR (Brigham & Women’s Hospital) did not have this code listed in the dataset; however, it is likely that this is due to how the data was pulled – it could be that this value was not included since it was the primary filter criteria for these patients.

Excluding the ICD-9 code for Ectodermal Dysplasia, eight of the seventeen HED patients had another diagnosis code within the Congenital Anomalies category (all eight were not known to have a NEMO

mutation). The most common diagnoses for HED patients, excluding those with a NEMO mutation, are listed in Table 4 below.

**Table 4: Congenital Abnormalities – Frequent Diagnoses**

Code	Description	Number of Patients	Patient Base	Average Age at Onset	Age Range
756.0	Congenital anomalies of skull and face bones	3	15	4	2 – 6

The frequency of this diagnosis – anomalies of the skull and face bones – is expected given the results of the review. HED patients are known to have craniofacial abnormalities. In this dataset, it appears this condition is generally diagnosed during early childhood.

## Symptoms, Signs, and Ill-Defined Conditions

Thirteen of the nineteen HED patients were coded with an ICD-9 diagnosis from the Symptoms, Signs, and Ill-Defined Conditions category, or nine of the fifteen non-NEMO patients. The most common diagnoses for HED patients, excluding those with a NEMO mutation, are listed in Table 5 below.

**Table 5: Symptoms, Signs, and Ill-Defined Conditions – Frequent Diagnoses**

Code	Description	Number of Patients	Patient Base	Average Age at Onset	Age Range
780.6	Fever	3	15	17	1 – 49
783.4	Lack of expected normal physiological development in childhood	3	15	5	2 – 11

A diagnosis of fever is consistent with HED’s cardinal feature of hypohidrosis. Since HED patients are unable to maintain their body heat through sweating, fevers are frequent throughout childhood and adult life, as is consistent with this claims data.

As presented in the literature review and registry analysis, HED patients often experience feeding problems and failure to thrive in infancy and below average body mass index during childhood. This factor, along with the phenotypic characteristics of HED, could be the reason for the frequency of the diagnosis code for abnormal physiological development in childhood.



## Diseases of the Respiratory System

Twelve of the nineteen HED patients were coded with an ICD-9 diagnosis from the Diseases of the Respiratory System category, or eight of the fifteen non-NEMO HED patients. While there were no common diagnoses in this category, the most common diagnosis sub-categories, excluding patients with a NEMO mutation, are listed in Table 6 below.

**Table 6: Diseases of the Respiratory System – Frequent Diagnosis Sub-categories**

Codes	Description	Number of Patients	Patient Base	Average Age at Onset	Age Range
460 – 466	Acute Respiratory Infections	3	15	5	2 – 11
490 – 496	Chronic Obstructive Pulmonary Disease And Allied Conditions	4	15	14	1 – 49
470 – 478	Other Diseases Of Upper Respiratory Tract	6	15	11	2 – 41

The frequency of respiratory conditions is consistent with analysis presented earlier – HED patients are at a higher risk for respiratory infections due to missing or abnormal mucous glands. The diagnoses associated with Acute Respiratory Infections most commonly consisted of acute pharyngitis, while the Chronic Obstructive Pulmonary Disease and Allied Conditions codes were most commonly related to asthma. The diagnoses associated with Other Diseases of Upper Respiratory Tract were generally some form of chronic sinusitis or allergic rhinitis.

## Diseases of the Skin and Subcutaneous Tissue

Thirteen of the nineteen HED patients were coded with an ICD-9 diagnosis from the Diseases of the Skin and Subcutaneous Tissue category. The most common diagnoses for HED patients, excluding those with a NEMO mutation, are listed in Table 7 below.

**Table 7: Diseases of the Skin and Subcutaneous Tissue – Frequent Diagnoses**

Code	Description	Number of Patients	Patient Base	Average Age at Onset	Age Range
691.8	Other atopic dermatitis and related conditions	3	15	18	2 – 50
692.9	Contact dermatitis and other eczema, unspecified cause	3	15	2	1 – 4

As consistent with earlier findings, HED patients commonly suffer from eczema and atopic dermatitis, as well as general dryness of the skin, due to the patients' lack of sweat glands.

Other patients had documented cases of abscesses and/or impetigo, which are not generally included in lists of common HED features. However, these diagnoses were only present for two patients and may have been unrelated to the phenotypic presentation of HED.

## Diseases of the Digestive System

Nine of the nineteen HED patients were coded with an ICD-9 diagnosis from the Diseases of the Digestive System category, or five of the fifteen non-NEMO patients. Diagnoses varied widely, and there were no frequent diagnosis codes or diagnosis sub-categories. The only shared diagnosis between two patients was the diagnosis code for other and unspecified noninfectious gastroenteritis and colitis (ICD-9 558.9). Consistent with earlier analysis, difficulties with the digestive tract are common in HED due to lack of development of mucous glands.

## Diseases of the Nervous System and Sense Organs

Nine of the nineteen HED patients were coded with an ICD-9 diagnosis from the Diseases of the Nervous System and Sense Organs, or five of the fifteen non-NEMO HED patients. While there were no common diagnoses, the most common diagnosis sub-categories, excluding patients with a NEMO mutation, are listed in Table 8 below.

**Table 8: Diseases of the Nervous System and Sense Organs – Frequent Diagnosis Sub-categories**

Codes	Description	Number of Patients	Patient Base	Average Age at Onset	Age Range
360 – 379	Disorders Of The Eye And Adnexa	3	15	2	2 – 11

Diagnoses within this category varied widely. Diagnoses within the Disorders of the Eye and Adnexa category included conjunctivitis, cataracts, and visual disturbances, and are likely not related to the clinical manifestations of HED. The only common diagnosis within the Diseases of the Nervous System and Sense Organs category was hearing loss (ICD-9 389; n=2). From my background research, I did not find hearing loss to be a common co-morbidity of HED, although it could be related to the build-up of wax and frequent ear infections that many HED patients experience.

## **Endocrine, Nutritional and Metabolic Diseases, and Immunity Disorders**

Eight of the nineteen HED patients were coded with an ICD-9 diagnosis from the Endocrine, Nutritional and Metabolic Diseases, and Immunity Disorders category, or four of the fifteen non-NEMO HED patients. Diagnoses varied widely, and there were no frequent diagnosis codes or diagnosis sub-categories. The only shared diagnosis between two patients was the diagnosis code for disorders of fluid electrolyte and acid-base balance (ICD-9 276). One patient was diagnosed with alkalosis (ICD-9 276.3) and the other with volume depletion (ICD-9 276.5). These problems were not mentioned in my background research for HED and may be unrelated to the disease phenotype.

## **Infectious and Parasitic Diseases**

Seven of the nineteen HED patients were coded with an ICD-9 diagnosis from the Infectious and Parasitic Diseases category, or three of the fifteen non-NEMO patients. Diagnoses varied widely, and there were no frequent diagnosis codes or diagnosis sub-categories. The only shared diagnoses between two patients were infectious colitis, enteritis, and gastroenteritis (ICD-9 009.0) and Streptococcal sore throat (ICD-9 558.9).

The patients diagnosed with infections colitis, enteritis, and gastroenteritis were the same two patients also diagnosed with non-infections gastroenteritis and colitis (ICD-9 558.9), as described in the Diseases of the Digestive System section previously.

The frequency of streptococcal sore throat could be related to the deficiency of mucous glands in the respiratory tract, as described previously. An alternative explanation might be that these patients have a mutation in the NEMO gene, instead of a mutation in the EDA gene (XLHED), which is more commonly associated with immune deficiency. Neither of these patients had undergone genetic testing to determine the genetic etiology of their disease.

## **Mental Disorders**

Five of the nineteen HED patients were coded with an ICD-9 diagnosis from the Mental Disorders category, or four of the fifteen non-NEMO HED patients. The most common diagnoses for HED patients, excluding those with a NEMO mutation, are listed in Table 9 below.

**Table 9: Mental Disorders – Frequent Diagnoses**

Code	Description	Number of Patients	Patient Base	Average Age at Onset	Age Range
315.9	Unspecified delay in development	3	15	8	3 – 12

As consistent with earlier findings, HED patients tend to have delays in normal childhood development. Three patients were also diagnosed with other mental disorders – including adjustment reaction, persistent mental disorders, and anxiety.

## Patient Profile

Despite limited data, I looked across diagnosis categories by patient in order to see whether a consistent patient profile – or a set of frequent diagnosis categories – could be developed for a patient with HED. I looked across diagnosis patterns by patient – a summary of this data is presented in Table 10 below.

**Table 10: Diagnosis Patterns by Patient**

Diagnosis Category	Patient Type	XLHED or genetic mutation unknown																	NEMO			
		Facility	CHB																	CHB		
			BWH	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
		44	54	2	5	7	11	12	13	13	13	15	19	21	40	70	5	12	27	27		
Congenital Anomalies			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Symptoms, Signs, And Ill-Defined Conditions			x				x	x	x	x	x		x	x		x	x	x	x	x	x	
Diseases Of The Respiratory System			x	x	x			x	x		x			x	x				x	x	x	
Diseases Of The Skin And Subcutaneous Tissue			x	x	x			x	x		x		x							x	x	
Supplementary Classification Of Factors Influencing Health Status And Contact With Health Services			x		x			x	x		x	x								x	x	
Diseases Of The Digestive System			x					x	x		x					x				x	x	
Diseases Of The Nervous System And Sense Organs			x					x	x		x					x				x	x	
Endocrine, Nutritional And Metabolic Diseases, And Immunity Disorders			x					x			x					x				x	x	
Infectious And Parasitic Diseases								x			x					x				x	x	
Diseases Of The Genitourinary System								x			x									x	x	
Injury And Poisoning			x					x			x										x	
Diseases Of The Blood And Blood-Forming Organs			x												x						x	
Diseases Of The Musculoskeletal System And Connective Tissue			x																		x	
Mental Disorders			x					x	x							x					x	
Supplementary Classification Of External Causes Of Injury And Poisoning			x					x													x	
Diseases Of The Circulatory System			x																		x	
Neoplasms			x																		x	
Certain Conditions Originating In The Perinatal Period																					x	

The HED patients with a NEMO mutation all experienced symptoms within multiple diagnosis categories, ranging from known HED characteristics such as diseases of the skin and respiratory system, to seemingly unrelated categories, such as diseases of the genitourinary system and diseases of the blood and blood-forming organs.

Within the non-NEMO HED patients, there is a clear division of patients with numerous and broad-ranging diagnoses, and those with very few diagnosis codes, regardless of treating facility. There was no correlation between age and number of diagnoses – although patients at both the low and the high end of the age spectrum tended to have fewer diagnoses than those in middle age range.

Five of the fifteen non-NEMO HED patients had diagnosis codes spanning eight or more categories. These patients all had codes for disorders affecting the respiratory system, skin/subcutaneous tissue, digestive system, nervous system, endocrine/metabolic/immunity disorders, and mental disorders. Most of these diagnoses fit within the known clinical manifestations of HED and are to be expected. The two categories that I would not have expected to be as common among the HED patient cohort were diseases of the digestive system and endocrine/metabolic/immunity disorders. These conditions could be unrelated to the HED, and given the small sample size, it is difficult to draw conclusions about the prevalence of these symptoms within the broader HED presentation.

The remaining ten non-NEMO HED patients all had diagnosis codes within three or fewer ICD-9 categories. The most common ICD-9 categories other than Congenital Anomalies were disorders of the respiratory system and of the skin and subcutaneous tissue. While these symptoms could be expected of patients suffering from HED, there was no consistency or pattern in how these patients were diagnosed. Many had a diagnosis in only one category or another, and there would be no method to identify these patients from other disorders affecting these systems based on claims data alone.

## Discussion

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### Study Limitations

There were several limitations of this study that could have accounted for the limited amount of patient data and ability to draw strong conclusions from the analysis. First, given the low estimated prevalence of the disease, the number of patients available for analysis was limited, preventing the generation of significant statistical measures. Second, the patient demographic and genetic distribution of HED patients in this small dataset may not be representative of HED patients in a broader geographical region. All of the patients in this study were treated at one of two facilities within the same major metropolitan area. There could be an abnormal proportion of patients in this geographical region with a particular genetic mutation that is associated with different phenotypic features from the average HED

patient, or large families with many affected individuals treated at these two facilities could also bias our results. While the papers analyzed in the literature review estimated that over 80% of cases of HED are due to a mutation in the EDA gene (XLHED), in this analysis, four of the nineteen patients with associated claims data had a NEMO mutation, one of the less common mutations of patients with HED. HED caused by a mutation in the NEMO gene is thought to have a slightly different phenotype than XLHED, and therefore, these patients were separated when analyzing patterns at the specific diagnosis code and diagnosis sub-category levels. Additionally, there could be a bias in the diagnosis and treatment patterns for patients at these facilities. Given that both of these facilities are major academic centers, diagnosis codes for these patients might be much more detailed and thorough than would be present in a dataset comprised of claims data from a physician offices or community hospitals. Finally, the databases utilized in this study did not contain a continuous, comprehensive record of each patient's medical history. It is possible that the comorbidities associated with HED were treated across multiple facilities, and therefore these databases with not include diagnoses for symptoms were treated earlier in life or at a different facility. For example, none of the HED patients were coded with the ICD-9 diagnosis for anodontia. A possible explanation for this finding could be that these patients had previously been diagnosed and treated for this condition by their dentist or other oral health specialist, and since this clinical feature was no longer symptomatic, anodontia was not coded as a diagnosis at the time of their hospital visit. Therefore, unless the patient had a thorough review of their medical history, including prior diagnoses and procedures perform, the diagnosis profile for these patients may contain none or few of the ICD-9 codes related to the hallmark features of the disease.

There are also broader limitations in studying treatment patterns of such a rare genetic disease. First, given the rarity of the disease, there could be low disease awareness among general practitioners, leading to underdiagnosis. Alternatively, given that the disease is inherited through a female carrier, many affected families may already be aware of their diagnosis and have accommodated for disease symptoms. Therefore, these patients would likely not need to visit a large medical center for management of their HED; instead, these hospital visits would more likely be related to new conditions or unrelated emergencies.

## **Data Limitations**

There were also inherent challenges with using claims data as the basis for our identification algorithm. Claims databases can be an excellent tool for clinical research. They often include larger patient

populations than available in a single EMR database, they contain a comprehensive record of a patient's medical history across healthcare providers and facilities, and the data is readily available from several information suppliers. However, claims data may not accurately reflect a patient's true clinical history. Several other epidemiological studies have attempted to measure the accuracy and reliability of research based on claims data.

A study published in April 2011 measured the validity of claims-based algorithms to identify outpatients with neutropenia. Several algorithms were developed based on the presence of one of the seven ICD-9 codes for neutropenia, and in some of the algorithms, the filter criteria also included the presence of a prescription for a drug indicated for neutropenia (G-CSF). While ICD-9 codes alone can identify inpatients suffering from neutropenia with a positive predictive value (PPV) of 97%, when these algorithms were tested on outpatient data, the PPV ranged from 3% to 56%, depending on the criteria used and severity of the disease. The investigators speculated that physicians might not necessarily code for neutropenia in the outpatient setting the neutropenia was asymptomatic or secondary to other health conditions.<sup>31</sup> This was also likely the case in our study, and the reason the patients in our cohort lacked an ICD-9 diagnosis code for the hallmark clinical features of HED.

Another study published in 1993 tested the accuracy of using claims data to identify patients at risk for ischemic heart disease. The study found that insurance claims data lacked the ability to identify more than half of patients with prognostic indicators of heart disease – such as congestive heart failure, mitral insufficiency, peripheral vascular disease, prior myocardial infarctions, and angina. Further, the investigators found that the claims data lacked altogether diagnosis codes for two key risk factors for heart disease – the ventricular ejection fraction and the number of diseased vessels. The authors concluded that claims data lacked important diagnostic and prognostic tools compared to medical record data, and should be used with caution when attempting to identify specific patient groups. This study shared several limitations with our study of HED – many patients in our cohort did not have a single diagnosis code related to the hallmark disease symptoms, and no diagnosis codes exist for HED or any of the specific genetic forms of the disease. The authors of this paper also suggested several ways to improve the usability of claims data for clinical research. Their recommendations include expanding and clarifying the definitions for each diagnosis code, aligning the coding process to parallel the clinical care process, and updating guidelines to promote coding practices that could be used to support clinical research and accurate patient characterization.<sup>32</sup>

A study published in early 2011 demonstrated similar findings for Rheumatoid Arthritis (RA). In this study, several algorithms based on claims data were tested for accuracy in identifying patients with RA. The algorithms consisted of various combinations of criteria, utilizing ICD-9 diagnosis codes, visits to a rheumatologist, and pharmacy claims data. Unlike the previous studies, the investigators reported that in this case RA was overdiagnosed when using ICD-9 codes alone, and when algorithms were enhanced to include pharmacy claims filters, the predictive performance improved from a PPV of 55.7% to 88.9%.<sup>33</sup>

Another study testing an identification algorithm for RA was able to dramatically improve the predictive value by mining narrative data in the patient's EMR. There are two types of data within an EMR. Codified data is stored in a structure format, and includes fields such as demographics, laboratory results, and billing codes. The second is narrative data, which is stored as freetext, and includes notes written by physicians or nurses. Since it is free-form, narrative data has the ability to store a much broader range of information, and can include much more detail on a patient's current symptoms and medical history. The investigators in this study found that when adding criteria based on natural language processing of narrative data within an EMR, the PPV of identification algorithms increased to 94%, compared to 88% using EMR codified data, and 19% using the RA billing code alone.<sup>34</sup> While the algorithms to identify RA are affected by overdiagnosis, as opposed to the underdiagnosis of HED, analyzing the narrative data within EMR's would likely uncover more HED patients within a given dataset, and provide more detailed and novel insights on disease history and treatment patterns.

## **Recommendations**

A major finding of this research is that HED patients are inconsistently coded with ICD-9 diagnosis codes for billing purposes. Although there was a small sample size of patients included in this analysis, there were no similarities in the codes or diagnosis categories among the patients studied. Given that the dataset was generated by physicians at major academic centers, which are more likely to have sophisticated claims coding processes than individual physician offices or community hospitals, the codes present in the i2b2 and RPDR databases are likely more extensive than the diagnosis codes available in a broader population. Unless claims classifications or guidelines change significantly to enhance their use in clinical research and patient classification, further studies of claims data are not likely to be helpful for epidemiological research and incidence studies of XLHED.



If further claims research is performed, it would be recommended to analyze other diagnosis codes aside from the code for Ectodermal Dysplasia. It is possible that patients could be identified without a clinical diagnosis of HED or billing diagnosis code for ED based solely on the presence of the HED cardinal features. Codes that could be explored in various combinations to identify patient cohorts for further chart reviews include:

- Hypotrichosis (sparseness of hair): alopecia (ICD-9: 704.0), abnormalities of the hair (ICD-9: 704.2), unspecified disease of hair and hair follicles (ICD-9: 704.9)
- Hypohidrosis (lack of sweat glands): anhidrosis (ICD-9: 705.0), fever (ICD-9: 780.6), dyshidrosis (ICD-9: 705.81) , unspecified disorder of sweat glands (ICD-9: 705.9)
- Hypodontia (absence/abnormal teeth): anodontia (ICD-9: 520.0), complete edentulism (ICD-9: 525.4), partial edentulism (ICD-9: 525.5), endosseous dental implant failure (ICD-9: 525.7), abnormalities of size and form of teeth (ICD-9: 520.2)
- Other common features:
  - Congenital anomalies of skull and face bones ICD-9: 756.0)
  - Respiratory diseases (ICD-9: 460 – 519)
  - Atopic dermatitis (ICD-9: 691.8) or eczema (692.9)
  - Congenital anomalies of skull and face bones (ICD-9: 756.0)

For example, the presence of two cardinal features, or one cardinal feature and two common features, might be used to filter to a list of HED candidates. If the patient chart lacks a clinical diagnosis of HED, a chart review conducted by a disease expert would be required to confirm a diagnosis.

An alternative approach that would provide a more thorough patient review and deeper analysis of a typical patient profile and common treatment trends would be to use natural language processing to search clinical notes and other narrative data to identify possible patients. Potential search criteria could include one or more of the following:

- (“hypohidrotic” OR “anhidrotic”) AND “ectodermal” AND “dysplasia”) OR “hed” or “aed”
- “anodontia” OR “hypodontia” OR OR “edentulous” OR “tooth” OR “teeth”
- “alopecia” OR “bald” OR (“sparse” AND “hair”)
- “anhidrosis” OR “hypohidrosis” OR “sweat” OR “hyperthermia” OR “fever”
- “ectodermal” AND “dysplasia”

As required for filters based on claims data, a chart review by a disease expert would also be required to confirm diagnosis, particularly notes where these search terms were present. However, given the clinical utility and freetext format of clinical notes, search criteria based on narrative text is more likely to return HED patients that would be missed using claims data or codified EMR data alone.

In conclusion, I was able to meet two of the three research goals, despite having a limited patient population for analysis. Based on the literature review, I developed a clinical phenotype that would identify XLHED patients in medical records and/or claims data. Using the NFED patient registry data, I was also able to identify characteristics that are unique to XLHED and could be used to distinguish XLHED patients from those suffering with other ectodermal dysplasias. From the registry analysis, I was also able to calculate statistics describing the prevalence of associated symptoms in a much larger patient population than previously studied. Additional work could be performed at a de-aggregated, patient-level, to gain new insights on disease presentation.

After analyzing the medical record and claims data at two major academic medical centers, I was able to identify 25 total patients, 19 of whom had associated claims data, to include in the patient cohort for the last part of this study. Since this number was too small of a base from which to develop an identification algorithm as originally planned, I instead analyzed descriptive statistics of their claims data in order to better understand how these patients flow through the healthcare system, and what identification criteria might be valuable for an investigator studying a larger patient population in the future. Given the inconsistencies in coding – and in some cases absence of coding altogether – this analysis also suggested that XLHED may be underdiagnosed or inconsistently diagnosed, and more detailed clinical, textual-level analysis could be required to provide clearer epidemiological insights. Further studies using different combinations of claims and/or narrative data filters are recommended to continue this epidemiological research and provide new insights into the diagnosis and treatment patterns of XLHED.

## **Appendix A: Research Methodology Presented to Partners IRB**

### Purpose

Understanding the true incidence and prevalence of diseases has tremendous value for the medical field, particularly for orphan diseases. Orphan diseases are rare disorders that only affect a minority of the population (in the US, the disorder must affect less than 200,000 people, or 1 in 1,500). However, there are no best practices published that provide a methodology for estimating the number of people with a particular disease. The purpose of this study is to develop a methodology for determining incidence and prevalence, using the pediatric orphan disease Hypohidrotic Ectodermal Dysplasia (HED) as a case study.

The goal of the research at Partner's Healthcare will be to develop a series of algorithms that could be applied to a claims database to estimate the number of patients with HED in the broader US population. These algorithms will be built to analyze fields such as gender, year of birth, diagnosis codes and procedure codes that are found in medical claims data to identify cases of HED. We plan to develop three algorithms. Algorithm 1 (A1) will have a high sensitivity (ability to identify positive cases), algorithm 2 (A2) will have a high specificity (minimize false positives), and algorithm 3 (A3) will have a balance of high sensitivity and specificity.

### Study Protocol / Research Methodology

*Step 1.* We will perform a query of all of the patients in the RPDR database with the ICD-9 code of 757.31 Ectodermal Dysplasia (ED). We believe there are approximately 80 patients with this diagnosis code in the RPDR database. Once the cohort is identified we will request the following of this cohort: gender, year of birth, diagnoses, procedures, and clinical notes, in order for Dr. Schneeweiss and MIT graduate student Julie Hermann to perform chart reviews on the ED patients to confirm whether the patient has the specific form of ED we are studying, Hypohidrotic Ectodermal Dysplasia (HED). Based on estimates in the medical literature, we anticipate that out of the 80 patients coded with ED, approximately 70 patients will have HED.

*Step 2.* Ms. Hermann will further study the charts on those patients confirmed to have HED to better understand the patient history with this disease. We will look at the corpus of data assembled over the entire record for each patient to determine what electronic "profile" children with HED have. This

analysis will allow us to identify potential inclusion criteria (i.e. diagnosis of “hypodontia”) that will be incorporated into our identification algorithms.

*Step 3.* We will then split the population of patients with confirmed HED into two sets of data. One group will be considered part of the TRAIN data set, and the second will be part of the TEST data set. In addition to the HED patients, we will also obtain a random sampling of non-HED patients from the RPDR database to serve as the control population. Half of these cases will be used within our TRAIN data set to train our algorithms, while the remaining half of the non-HED patients be used as part of the TEST data set. The data elements pulled for the control cases will include gender, year of birth, diagnosis codes, and procedure codes, but not include any patient identifier information.

*Step 4.* Using the TRAIN dataset which will include 70% of the true HED cases plus half of the controls, three algorithms will be produced (A1, A2, A3). Ms. Hermann will develop an algorithm (A1) that correctly identifies as many of the true HED patients as possible.

*Step 5.* After the initial A1 algorithm is generated the false positives cases will be reviewed (patients in the control group without HED). The entire record of these false positive cases will be reviewed by Dr. Schneeweiss and Ms. Hermann to confirm that they truly do not have HED, and to better understand what exclusion criteria should be added to the algorithm to lower the number of false positives. Ms. Hermann will incorporate these exclusion criteria into the algorithm and repeat Step 5 for A1 until we develop an algorithm maximizing its sensitivity in positively identifying patients with HED.

*Step 6.* Ms. Hermann will repeat Step 5, this time focusing on achieving a high specificity (minimizing false positives) to develop A2.

*Step 7.* Ms. Hermann will repeat Step 5, this time focusing on a balance of specificity and sensitivity to develop A3. .

*Step 8.* The remaining half of the control patients (obtained in step 3) and the remaining 30% of true HED patients will be used to evaluate the final algorithms (A1,A2 and A3)

*Step 9.* The cases of HED identified with these algorithms will be evaluated and determined to be either cases of HED (part of the 30% of cases from the cohort) or “false positive”. Dr. Schneeweiss and Ms. Hermann will perform chart reviews on the false positive patients to confirm they truly do not have HED, and that our sensitivity and specificity measurements are accurate.

The outcome of our research will be three algorithms with a tested sensitivity and specificity that can be *applied to claims databases to identify the number of patients with HED.*

*As a separate phase of our research, we will apply A1, A2, and A3 to a national claims database that contains a patient population representative of the broader US population. This will give us an estimate of the incidence and prevalence of HED in the US population. None of the temporary data sets that we used to develop the algorithms will be retained. We will only use the set of inclusion/exclusion criteria that were built into the A1, A2, A3 queries will be used in our subsequent research.*

### Risks/Privacy Issues for Subjects

The proposed use of this data presents no more than minimal risk to the privacy of individuals. To do this study, we must obtain some amount of information to train the algorithm. The variables described in this protocol are the minimum needed to do so, and all information queried from the RPDR database will be de-identified before being reviewed by non-Partners personnel. The algorithms will be developed based on an extract of RPDR consisting of only gender, year of birth, procedure and diagnosis codes. To confirm the diagnosis of HED a chart review must be performed; however, the charts will be de-identified before being reviewed by non-Partners personnel, and will only performed on patients diagnosed with Ectodermal Dysplasia, or with patients suspected to have Hypohidrotic Ectodermal Dysplasia based on our identification algorithm.

The research could not practicably be conducted without the waiver of informed consent and authorization because it is impractical to obtain the number of consents needed for the large sample size required to train the algorithm.

The research could not practicably be conducted without access to and use of protected health information because the algorithms depend on the medical record to identify cases of HED.

Waiving informed consent would not adversely affect a subject's rights or welfare because we will not be reaching out to, contacting, or otherwise changing or affecting anything regarding the patient's clinical care.

### Other Research & IRB Approvals

Julie Hermann is simultaneously seeking MIT approval for both this IRB protocol as well as a similarly structured study at Children's Hospital of Boston. Dr. Richard Cohen is serving as the faculty sponsor for the MIT IRB protocol. Dr. Jonathan Bickel is the PI for the study at Children's Hospital of Boston.

In preparation for the algorithm design, Julie Hermann will be studying the NFED Ectodermal Dysplasia Registry to understand common symptoms of HED, and how those differ from other forms of ED. This data is only available in aggregate (not at the patient-level), and patients voluntarily fill out the survey for use by any researcher who uses the site. Therefore, an IRB protocol is not necessary.

#### Conflict of Interest / Financial Disclosures

Edimer Pharmaceuticals is providing a \$5,000 tuition subsidy to Julie Hermann for her research into the incidence of HED.

## Appendix B: HED Diagnosis Criteria

Patient #	
Diagnosis Decision	
<b>Hallmark Features</b>	
Reduced Sweating	
Missing/abnormal teeth	
Sparse hair on scalp & eyebrows	
<b>Other common symptoms of HED</b>	
Chronic nasal drainage	
Eczema / atopic dermatitis	
Dry skin	
Reduced saliva/dry mouth	
Raspy / hoarse voice	
Periorbital hyperpigmentation	
Heat intolerance /febrile seizures	
Depressed nasal bridge ("saddle nose")	
Sinus infections	
<b>Related ICD-9 codes</b>	
520- teeth	
705- sweat glands	
<b>Symptoms common to non-HED ED (other forms of Ectodermal Dysplasia)</b>	
Cleft palate / lip	
Limb/finger/toe issues - missing, extra, small, or fused	
Onychodysplasia – unusual nails	

## Appendix C: Claims Data Detail

Diagnosis	Patient Count	Average Age at Onset	Min Age at Onset	Max Age at Onset
<b>Certain Conditions Originating In The Perinatal Period</b>				
<b>Other Conditions Originating In The Perinatal Period</b>				
Infections specific to the perinatal period				
771.1				
Congenital cytomegalovirus infection	1	2	2	2
NEMO/EDAR mutation	1	2	2	2
<b>Congenital Anomalies</b>				
<b>Congenital Anomalies</b>				
Chromosomal anomalies				
758.81				
Other conditions due to sex chromosome anomalies	3	18	6	25
NEMO/EDAR mutation	3	18	6	25
Congenital anomalies of ear face and neck				
744.89				
Other specified congenital anomalies of face and neck	1	1	1	1
XLHED or genetic mutation unknown	1	1	1	1
Congenital anomalies of eye				
743				
Congenital anomalies of eye	1	7	7	7
NEMO/EDAR mutation	1	7	7	7
743.58				
Vascular anomalies, congenital	1	7	7	7
NEMO/EDAR mutation	1	7	7	7
Congenital anomalies of genital organs				
752.51				
Undescended testis	1	3	3	3
XLHED or genetic mutation unknown	1	3	3	3
Congenital anomalies of the integument				
757.1				
Ichthyosis congenita	1	1	1	1
XLHED or genetic mutation unknown	1	1	1	1
757.31				
Congenital ectodermal dysplasia	17	9	1	57
XLHED or genetic mutation unknown	13	10	1	57
NEMO/EDAR mutation	4	8	3	16
757.39				
Other specified congenital anomalies of skin	2	14	2	26
XLHED or genetic mutation unknown	1	2	2	2
NEMO/EDAR mutation	1	26	26	26
757.9				
Unspecified congenital anomaly of the integument	1	10	10	10
NEMO/EDAR mutation	1	10	10	10
Other and unspecified congenital anomalies				
759.89				
Other specified anomalies	3	9	2	22
XLHED or genetic mutation unknown	1	2	2	2
NEMO/EDAR mutation	2	13	3	22
Other congenital anomalies of digestive system				
751.2				
Atresia and stenosis of large intestine, rectum, and anal canal, congenital	1	22	22	22
NEMO/EDAR mutation	1	22	22	22
751.5				
Other congenital anomalies of intestine	1	3	3	3
NEMO/EDAR mutation	1	3	3	3
Other congenital anomalies of limbs				
755.64				
Congenital deformity of knee (joint)	1	10	10	10



NEMO/EDAR mutation	1	10	10	10
Other congenital anomalies of nervous system				
742.4				
Other specified congenital anomalies of brain	1	7	7	7
XLHED or genetic mutation unknown	1	7	7	7
742.9				
Unspecified congenital anomaly of brain, spinal cord, and nervous system	1	4	4	4
XLHED or genetic mutation unknown	1	4	4	4
Other congenital musculoskeletal anomalies				
756.0				
Congenital anomalies of skull and face bones	3	4	2	6
XLHED or genetic mutation unknown	3	4	2	6
756.11				
Spondylolysis, congenital, lumbosacral region	1	27	27	27
NEMO/EDAR mutation	1	27	27	27
756.12				
Spondylolisthesis, congenital	1	27	27	27
NEMO/EDAR mutation	1	27	27	27
<b>Diseases Of The Blood And Blood-Forming Organs</b>				
<b>Diseases Of The Blood And Blood-Forming Organs</b>				
Acquired hemolytic anemias				
283.9				
Acquired hemolytic anemia, unspecified	1	7	7	7
NEMO/EDAR mutation	1	7	7	7
Diseases of white blood cells				
288.00				
Neutropenia, unspecified	1	8	8	8
NEMO/EDAR mutation	1	8	8	8
Iron deficiency anemias				
280.9				
Iron deficiency anemia, unspecified	1	25	25	25
NEMO/EDAR mutation	1	25	25	25
Other and unspecified anemias				
285.21				
Anemia in chronic kidney disease.	1	23	23	23
NEMO/EDAR mutation	1	23	23	23
285.9				
Anemia, unspecified	1	22	22	22
NEMO/EDAR mutation	1	22	22	22
Other diseases of blood and blood-forming organs				
289.9				
Unspecified diseases of blood and blood-forming organs	2	27	7	47
XLHED or genetic mutation unknown	1	47	47	47
NEMO/EDAR mutation	1	7	7	7
Purpura and other hemorrhagic conditions				
287.2				
Other nonthrombocytopenic purpuras	2	28	8	47
XLHED or genetic mutation unknown	1	47	47	47
NEMO/EDAR mutation	1	8	8	8
287.4				
Secondary thrombocytopenia	1	25	25	25
NEMO/EDAR mutation	1	25	25	25
287.9				
Unspecified hemorrhagic conditions	1	6	6	6
XLHED or genetic mutation unknown	1	6	6	6
<b>Diseases Of The Circulatory System</b>				
<b>Cerebrovascular Disease</b>				
Other and ill-defined cerebrovascular disease				
437.6				
Nonpyogenic thrombosis of intracranial venous sinus	1	25	25	25
NEMO/EDAR mutation	1	25	25	25
437.9				
Unspecified cerebrovascular disease	1	6	6	6

NEMO/EDAR mutation	1	6	6	6
Diseases Of Arteries, Arterioles, And Capillaries				
Aortic aneurysm and dissection				
441.9				
Aortic aneurysm of unspecified site without mention of rupture	1	6	6	6
NEMO/EDAR mutation	1	6	6	6
Atherosclerosis				
440.20				
Atherosclerosis of native arteries of the extremities, unspecified	1	49	49	49
XLHED or genetic mutation unknown	1	49	49	49
Other peripheral vascular disease				
443.81				
Peripheral angiopathy in diseases classified elsewhere	1	49	49	49
XLHED or genetic mutation unknown	1	49	49	49
443.9				
Peripheral vascular disease, unspecified	1	49	49	49
XLHED or genetic mutation unknown	1	49	49	49
Polyarteritis nodosa and allied conditions				
446.6				
Thrombotic microangiopathy	1	47	47	47
XLHED or genetic mutation unknown	1	47	47	47
Diseases Of Veins And Lymphatics, And Other Diseases Of Circulatory System				
Hypotension				
458.0				
Orthostatic hypotension	1	26	26	26
NEMO/EDAR mutation	1	26	26	26
458.9				
Hypotension, unspecified	1	4	4	4
NEMO/EDAR mutation	1	4	4	4
Other disorders of circulatory system				
459.10				
Postphlebotic syndrome without complications	1	49	49	49
XLHED or genetic mutation unknown	1	49	49	49
459.81				
Venous (peripheral) insufficiency, unspecified	1	49	49	49
XLHED or genetic mutation unknown	1	49	49	49
459.89				
Other specified circulatory system disorders	1	8	8	8
NEMO/EDAR mutation	1	8	8	8
Other venous embolism and thrombosis				
453.9				
Embolism and thrombosis of unspecified site	1	47	47	47
XLHED or genetic mutation unknown	1	47	47	47
Varicose veins of lower extremities				
454.1				
Varicose veins of lower extremities with inflammation	1	47	47	47
XLHED or genetic mutation unknown	1	47	47	47
Hypertensive Disease				
Essential hypertension				
401.1				
Benign essential hypertension	1	49	49	49
XLHED or genetic mutation unknown	1	49	49	49
401.9				
Unspecified essential hypertension	3	24	4	49
XLHED or genetic mutation unknown	1	49	49	49
NEMO/EDAR mutation	2	12	4	20
Hypertensive kidney disease				
403.90				
Hypertensive renal disease, unspecified, without mention of renal failure	2	12	5	19
NEMO/EDAR mutation	2	12	5	19
403.91				
Hypertensive renal disease, unspecified, with renal failure	1	22	22	22
NEMO/EDAR mutation	1	22	22	22

Secondary hypertension				
405.99				
Other unspecified secondary hypertension	1	5	5	5
NEMO/EDAR mutation	1	5	5	5
Other Forms Of Heart Disease				
Acute and subacute endocarditis				
421.0				
Acute and subacute bacterial endocarditis	1	22	22	22
NEMO/EDAR mutation	1	22	22	22
Ill-defined descriptions and complications of heart disease				
429.9				
Heart disease, unspecified	1	6	6	6
NEMO/EDAR mutation	1	6	6	6
Other diseases of endocardium				
424.90				
Endocarditis, valve unspecified, unspecified cause	1	22	22	22
NEMO/EDAR mutation	1	22	22	22
Diseases Of The Digestive System				
Appendicitis				
Acute appendicitis				
540.1				
Acute appendicitis with peritoneal abscess	1	27	27	27
NEMO/EDAR mutation	1	27	27	27
Diseases Of Esophagus, Stomach, And Duodenum				
Diseases of esophagus				
530.81				
Esophageal reflux	4	9	2	22
XLHED or genetic mutation unknown	1	2	2	2
NEMO/EDAR mutation	3	11	4	22
Disorders of function of stomach				
536.2				
Persistent vomiting	1	5	5	5
NEMO/EDAR mutation	1	5	5	5
536.3				
Gastroparesis	1	5	5	5
NEMO/EDAR mutation	1	5	5	5
536.41				
Infection of gastrostomy	1	3	3	3
NEMO/EDAR mutation	1	3	3	3
536.49				
Other gastrostomy complications	1	7	7	7
NEMO/EDAR mutation	1	7	7	7
536.8				
Dyspepsia and other specified disorders of function of stomach	1	5	5	5
NEMO/EDAR mutation	1	5	5	5
Duodenal ulcer				
532.90				
Duodenal ulcer, unspecified as acute or chronic, without hemorrhage or perforation, without mention of obstruction	1	2	2	2
NEMO/EDAR mutation	1	2	2	2
Gastric ulcer				
531.90				
Gastric ulcer, unspecified as acute or chronic, without mention of hemorrhage or perforation, without mention of obstruction	1	2	2	2
NEMO/EDAR mutation	1	2	2	2
Gastritis and duodenitis				
535.10				
Atrophic gastritis, without mention of hemorrhage	1	5	5	5
NEMO/EDAR mutation	1	5	5	5
535.50				
Unspecified gastritis and gastroduodenitis, without mention of hemorrhage	2	9	4	13
XLHED or genetic mutation unknown	1	13	13	13
NEMO/EDAR mutation	1	4	4	4

535.60				
Duodenitis, without mention of hemorrhage	1	2	2	2
NEMO/EDAR mutation	1	2	2	2
Diseases Of Oral Cavity, Salivary Glands, And Jaws				
Diseases of hard tissues of teeth				
521.0				
Dental caries	1	12	12	12
NEMO/EDAR mutation	1	12	12	12
521.00				
Dental caries, unspecified	1	7	7	7
XLHED or genetic mutation unknown	1	7	7	7
Diseases of the jaws				
526.1				
Fissural cysts of jaw	1	6	6	6
XLHED or genetic mutation unknown	1	6	6	6
526.2				
Other cysts of jaws	1	6	6	6
XLHED or genetic mutation unknown	1	6	6	6
Diseases of the oral soft tissues excluding lesions specific for gingiva and tongue				
528.9				
Other and unspecified diseases of the oral soft tissues	1	19	19	19
NEMO/EDAR mutation	1	19	19	19
Noninfective Enteritis And Colitis				
Other and unspecified noninfectious gastroenteritis and colitis				
558.3				
Allergic gastroenteritis and colitis	1	5	5	5
NEMO/EDAR mutation	1	5	5	5
558.9				
Other and unspecified noninfectious gastroenteritis and colitis	3	2	2	2
XLHED or genetic mutation unknown	2	2	2	2
NEMO/EDAR mutation	1	2	2	2
Regional enteritis				
555.9				
Regional enteritis of unspecified site	1	4	4	4
NEMO/EDAR mutation	1	4	4	4
Ulcerative enterocolitis				
556.5				
Left-sided ulcerative (chronic) colitis	1	5	5	5
NEMO/EDAR mutation	1	5	5	5
556.6				
Universal ulcerative (chronic) colitis	1	4	4	4
NEMO/EDAR mutation	1	4	4	4
Other Diseases Of Digestive System				
Cholelithiasis				
574.20				
Calculus of gallbladder without mention of cholecystitis, without mention of obstruction	1	25	25	25
NEMO/EDAR mutation	1	25	25	25
Chronic liver disease and cirrhosis				
571.8				
Other chronic nonalcoholic liver disease	1	49	49	49
XLHED or genetic mutation unknown	1	49	49	49
Gastrointestinal hemorrhage				
578.1				
Blood in stool	1	4	4	4
NEMO/EDAR mutation	1	4	4	4
Intestinal malabsorption				
579.8				
Other specified intestinal malabsorption	1	2	2	2
NEMO/EDAR mutation	1	2	2	2
579.9				
Unspecified intestinal malabsorption	1	3	3	3
NEMO/EDAR mutation	1	3	3	3

Other disorders of gallbladder				
575.6				
Cholesterolosis of gallbladder	1	49	49	49
XLHED or genetic mutation unknown	1	49	49	49
Other disorders of liver				
573.3				
Hepatitis, unspecified	1	49	49	49
XLHED or genetic mutation unknown	1	49	49	49
Other Diseases Of Intestines And Peritoneum				
0				
565.0				
Anal fissure	1	3	3	3
NEMO/EDAR mutation	1	3	3	3
Abscess of anal and rectal regions				
566				
Abscess of anal and rectal regions	1	3	3	3
NEMO/EDAR mutation	1	3	3	3
Anal fissure and fistula				
565.1				
Anal fistula	1	3	3	3
NEMO/EDAR mutation	1	3	3	3
Functional digestive disorders not elsewhere classified				
564.0				
Constipation	2	8	3	13
XLHED or genetic mutation unknown	1	3	3	3
NEMO/EDAR mutation	1	13	13	13
564.00				
Constipation, unspecified	2	4	3	5
XLHED or genetic mutation unknown	1	3	3	3
NEMO/EDAR mutation	1	5	5	5
564.09				
Other constipation	1	5	5	5
NEMO/EDAR mutation	1	5	5	5
564.1				
Irritable bowel syndrome	1	9	9	9
NEMO/EDAR mutation	1	9	9	9
564.89				
Other functional disorders of intestine	1	6	6	6
NEMO/EDAR mutation	1	6	6	6
Intestinal obstruction without mention of hernia				
560.1				
Paralytic ileus	1	22	22	22
NEMO/EDAR mutation	1	22	22	22
560.9				
Unspecified intestinal obstruction	1	3	3	3
NEMO/EDAR mutation	1	3	3	3
Other disorders of intestine				
569.3				
Hemorrhage of rectum and anus	2	15	11	18
NEMO/EDAR mutation	2	15	11	18
569.41				
Ulcer of anus and rectum	1	19	19	19
NEMO/EDAR mutation	1	19	19	19
569.49				
Other specified disorders of rectum and anus	1	9	9	9
NEMO/EDAR mutation	1	9	9	9
569.82				
Ulceration of intestine	1	2	2	2
NEMO/EDAR mutation	1	2	2	2
569.9				
Unspecified disorder of intestine	1	4	4	4
NEMO/EDAR mutation	1	4	4	4
Diseases Of The Genitourinary System				

<b>Diseases Of Male Genital Organs</b>				
Redundant prepuce and phimosis				
605				
Redundant prepuce and phimosis	1	1	1	1
XLHED or genetic mutation unknown	1	1	1	1
Nephritis, Nephrotic Syndrome, And Nephrosis				
Chronic glomerulonephritis				
582.9				
Chronic glomerulonephritis with unspecified pathological lesion in kidney	1	20	20	20
NEMO/EDAR mutation	1	20	20	20
Chronic kidney disease (ckd)				
585				
Chronic kidney disease (CKD)	1	22	22	22
NEMO/EDAR mutation	1	22	22	22
585.6				
End stage renal disease	1	22	22	22
NEMO/EDAR mutation	1	22	22	22
585.9				
Chronic kidney disease, unspecified	1	24	24	24
NEMO/EDAR mutation	1	24	24	24
Disorders resulting from impaired renal function				
588.81				
Secondary hyperparathyroidism (of renal origin)	1	24	24	24
NEMO/EDAR mutation	1	24	24	24
588.89				
Other specified disorders resulting from impaired renal function	1	5	5	5
NEMO/EDAR mutation	1	5	5	5
Renal failure unspecified				
586				
Renal failure, unspecified	1	22	22	22
NEMO/EDAR mutation	1	22	22	22
Other Diseases Of Urinary System				
Hydronephrosis				
591				
Hydronephrosis	1	5	5	5
NEMO/EDAR mutation	1	5	5	5
Infections of kidney				
590.2				
Renal and perinephric abscess	1	21	21	21
NEMO/EDAR mutation	1	21	21	21
Other disorders of kidney and ureter				
593.9				
Unspecified disorder of kidney and ureter	1	19	19	19
NEMO/EDAR mutation	1	19	19	19
Other disorders of urethra and urinary tract				
599.0				
Urinary tract infection, site not specified	3	10	2	22
XLHED or genetic mutation unknown	1	2	2	2
NEMO/EDAR mutation	2	14	5	22
Diseases Of The Musculoskeletal System And Connective Tissue				
Arthropathies And Related Disorders				
Internal derangement of knee				
717.6				
Loose body in knee	1	10	10	10
NEMO/EDAR mutation	1	10	10	10
Other and unspecified arthropathies				
716.50				
Unspecified polyarthropathy or polyarthritis, site unspecified	1	5	5	5
NEMO/EDAR mutation	1	5	5	5
716.60				
Unspecified monoarthritis, site unspecified	1	10	10	10
NEMO/EDAR mutation	1	10	10	10
Other and unspecified disorders of joint				

719.06				
Effusion of lower leg joint	2	5	4	5
NEMO/EDAR mutation	2	5	4	5
719.07				
Effusion of ankle and foot joint	1	7	7	7
NEMO/EDAR mutation	1	7	7	7
719.40				
Pain in joint, site unspecified	1	10	10	10
NEMO/EDAR mutation	1	10	10	10
719.41				
Pain in joint involving shoulder region	1	22	22	22
NEMO/EDAR mutation	1	22	22	22
719.45				
Pain in joint involving pelvic region and thigh	1	9	9	9
NEMO/EDAR mutation	1	9	9	9
719.46				
Pain in joint involving lower leg	2	12	10	14
NEMO/EDAR mutation	2	12	10	14
Rheumatoid arthritis and other inflammatory polyarthropathies				
714.30				
Polyarticular juvenile rheumatoid arthritis, chronic or unspecified	1	5	5	5
NEMO/EDAR mutation	1	5	5	5
714.33				
Monoarticular juvenile rheumatoid arthritis	1	5	5	5
NEMO/EDAR mutation	1	5	5	5
Dorsopathies				
Intervertebral disc disorders				
722.92				
Other and unspecified disc disorder of thoracic region	2	25	22	27
NEMO/EDAR mutation	2	25	22	27
Other and unspecified disorders of back				
724.2				
Lumbago	1	16	16	16
NEMO/EDAR mutation	1	16	16	16
724.5				
Backache, unspecified	2	22	17	26
NEMO/EDAR mutation	2	22	17	26
Other disorders of cervical region				
723.5				
Torticollis, unspecified	1	6	6	6
NEMO/EDAR mutation	1	6	6	6
Osteopathies, Chondropathies, And Acquired Musculoskeletal Deformities				
Curvature of spine				
737.20				
Lordosis (acquired) (postural)	1	11	11	11
NEMO/EDAR mutation	1	11	11	11
737.31				
Resolving infantile idiopathic scoliosis	1	3	3	3
NEMO/EDAR mutation	1	3	3	3
Osteochondropathies				
732.7				
Osteochondritis dissecans	1	10	10	10
NEMO/EDAR mutation	1	10	10	10
Osteomyelitis periostitis and other infections involving bone				
730.00				
Acute osteomyelitis, site unspecified	1	25	25	25
NEMO/EDAR mutation	1	25	25	25
730.08				
Acute osteomyelitis involving other specified sites	1	18	18	18
NEMO/EDAR mutation	1	18	18	18
730.16				
Chronic osteomyelitis involving lower leg	1	49	49	49
XLHED or genetic mutation unknown	1	49	49	49

730.18				
Chronic osteomyelitis involving other specified sites	1	17	17	17
NEMO/EDAR mutation	1	17	17	17
730.2				
Unspecified osteomyelitis	1	18	18	18
NEMO/EDAR mutation	1	18	18	18
730.20				
Unspecified osteomyelitis, site unspecified	1	16	16	16
NEMO/EDAR mutation	1	16	16	16
730.21				
Unspecified osteomyelitis involving shoulder region	1	21	21	21
NEMO/EDAR mutation	1	21	21	21
730.28				
Unspecified osteomyelitis involving other specified sites	2	22	16	27
NEMO/EDAR mutation	2	22	16	27
Other disorders of bone and cartilage				
733				
Other disorders of bone and cartilage	1	5	5	5
NEMO/EDAR mutation	1	5	5	5
733.00				
Osteoporosis, unspecified	1	9	9	9
NEMO/EDAR mutation	1	9	9	9
733.09				
Other osteoporosis	1	5	5	5
NEMO/EDAR mutation	1	5	5	5
733.90				
Disorder of bone and cartilage, unspecified	2	12	5	19
NEMO/EDAR mutation	2	12	5	19
Rheumatism, Excluding The Back				
Disorders of muscle ligament and fascia				
728.85				
Spasm of muscle	1	2	2	2
XLHED or genetic mutation unknown	1	2	2	2
728.89				
Other disorder of muscle, ligament, and fascia	1	18	18	18
NEMO/EDAR mutation	1	18	18	18
Other disorders of soft tissues				
729.5				
Pain in limb	2	15	4	26
NEMO/EDAR mutation	2	15	4	26
Other disorders of synovium tendon and bursa				
727.00				
Synovitis and tenosynovitis, unspecified	1	10	10	10
NEMO/EDAR mutation	1	10	10	10
727.09				
Other synovitis and tenosynovitis	1	10	10	10
NEMO/EDAR mutation	1	10	10	10
727.81				
Contracture of tendon (sheath)	1	15	15	15
NEMO/EDAR mutation	1	15	15	15
Diseases Of The Nervous System And Sense Organs				
Diseases Of The Ear And Mastoid Process				
Hearing loss				
389.10				
Sensorineural hearing loss, unspecified	1	17	17	17
NEMO/EDAR mutation	1	17	17	17
389.11				
Sensory hearing loss, bilateral	1	12	12	12
XLHED or genetic mutation unknown	1	12	12	12
389.2				
Mixed conductive and sensorineural hearing loss	1	17	17	17
NEMO/EDAR mutation	1	17	17	17
389.8				



Other specified forms of hearing loss	1	5	5	5
NEMO/EDAR mutation	1	5	5	5
<b>389.9</b>				
Unspecified hearing loss	2	17	8	26
XLHED or genetic mutation unknown	1	8	8	8
NEMO/EDAR mutation	1	26	26	26
<b>Nonsuppurative otitis media and eustachian tube disorders</b>				
<b>381.10</b>				
Chronic serous otitis media, simple or unspecified	2	9	2	16
XLHED or genetic mutation unknown	1	2	2	2
NEMO/EDAR mutation	1	16	16	16
<b>381.20</b>				
Chronic mucoid otitis media, simple or unspecified	1	17	17	17
NEMO/EDAR mutation	1	17	17	17
<b>381.4</b>				
Nonsuppurative otitis media, not specified as acute or chronic	1	9	9	9
NEMO/EDAR mutation	1	9	9	9
<b>Other disorders of ear</b>				
<b>388.69</b>				
Other otorrhea	1	17	17	17
NEMO/EDAR mutation	1	17	17	17
<b>Suppurative and unspecified otitis media</b>				
<b>382.00</b>				
Acute suppurative otitis media without spontaneous rupture of ear drum	1	7	7	7
NEMO/EDAR mutation	1	7	7	7
<b>382.9</b>				
Unspecified otitis media	3	11	7	17
NEMO/EDAR mutation	3	11	7	17
<b>Disorders Of The Eye And Adnexa</b>				
<b>Cataract</b>				
<b>366.9</b>				
Unspecified cataract	1	11	11	11
XLHED or genetic mutation unknown	1	11	11	11
<b>Chorioretinal inflammations scars and other disorders of choroid</b>				
<b>363.20</b>				
Chorioretinitis, unspecified	1	25	25	25
NEMO/EDAR mutation	1	25	25	25
<b>Disorders of conjunctiva</b>				
<b>372.30</b>				
Conjunctivitis, unspecified	1	2	2	2
XLHED or genetic mutation unknown	1	2	2	2
<b>Disorders of refraction and accommodation</b>				
<b>367.0</b>				
Hypermetropia	2	8	7	8
NEMO/EDAR mutation	2	8	7	8
<b>367.20</b>				
Astigmatism, unspecified	1	8	8	8
NEMO/EDAR mutation	1	8	8	8
<b>Other disorders of eye</b>				
<b>379.41</b>				
Anisocoria	1	25	25	25
NEMO/EDAR mutation	1	25	25	25
<b>379.43</b>				
Mydriasis (persistent), not due to mydriatics	1	25	25	25
NEMO/EDAR mutation	1	25	25	25
<b>Other disorders of eyelids</b>				
<b>374.30</b>				
Ptosis of eyelid, unspecified	1	25	25	25
NEMO/EDAR mutation	1	25	25	25
<b>Other retinal disorders</b>				
<b>362.60</b>				
Peripheral retinal degeneration, unspecified	1	25	25	25
NEMO/EDAR mutation	1	25	25	25

362.81				
Retinal hemorrhage	1	25	25	25
NEMO/EDAR mutation	1	25	25	25
Retinal detachments and defects				
361.81				
Traction detachment of retina	1	25	25	25
NEMO/EDAR mutation	1	25	25	25
361.89				
Other forms of retinal detachment	1	25	25	25
NEMO/EDAR mutation	1	25	25	25
Strabismus and other disorders of binocular eye movements				
378.00				
Esotropia, unspecified	1	6	6	6
NEMO/EDAR mutation	1	6	6	6
378.20				
Intermittent heterotropia, unspecified	1	4	4	4
NEMO/EDAR mutation	1	4	4	4
378.22				
Intermittent esotropia, alternating	2	15	5	25
NEMO/EDAR mutation	2	15	5	25
378.53				
Fourth or trochlear nerve palsy	1	25	25	25
NEMO/EDAR mutation	1	25	25	25
378.54				
Sixth or abducens nerve palsy	1	25	25	25
NEMO/EDAR mutation	1	25	25	25
Visual disturbances				
368.2				
Diplopia	2	14	3	25
XLHED or genetic mutation unknown	1	3	3	3
NEMO/EDAR mutation	1	25	25	25
Disorders Of The Peripheral Nervous System				
Facial nerve disorders				
351.9				
Facial nerve disorder, unspecified	1	25	25	25
NEMO/EDAR mutation	1	25	25	25
Inflammatory and toxic neuropathy				
357.2				
Polyneuropathy in diabetes	1	49	49	49
XLHED or genetic mutation unknown	1	49	49	49
Myoneural disorders				
358.8				
Other specified myoneural disorders	1	2	2	2
XLHED or genetic mutation unknown	1	2	2	2
Trigeminal nerve disorders				
350.8				
Other specified trigeminal nerve disorders	1	25	25	25
NEMO/EDAR mutation	1	25	25	25
Hereditary And Degenerative Diseases Of The Central Nervous System				
Other diseases of spinal cord				
336.9				
Unspecified disease of spinal cord	1	16	16	16
NEMO/EDAR mutation	1	16	16	16
Other extrapyramidal disease and abnormal movement disorders				
333.94				
Restless legs syndrome (RLS)	1	25	25	25
NEMO/EDAR mutation	1	25	25	25
333.99				
Other extrapyramidal diseases and abnormal movement disorders	1	25	25	25
NEMO/EDAR mutation	1	25	25	25
Inflammatory Diseases Of The Central Nervous System				
Intracranial and intraspinal abscess				
324.0				

Intracranial abscess	1	26	26	26
NEMO/EDAR mutation	1	26	26	26
<b>324.1</b>				
Intraspinal abscess	1	22	22	22
NEMO/EDAR mutation	1	22	22	22
<b>Other Disorders Of The Central Nervous System</b>				
<b>Epilepsy</b>				
<b>345.80</b>				
Other forms of epilepsy, without mention of intractable epilepsy	1	5	5	5
NEMO/EDAR mutation	1	5	5	5
<b>345.81</b>				
Other forms of epilepsy, with intractable epilepsy	1	6	6	6
NEMO/EDAR mutation	1	6	6	6
<b>Other and unspecified disorders of the nervous system</b>				
<b>349.9</b>				
Unspecified disorders of nervous system	1	11	11	11
NEMO/EDAR mutation	1	11	11	11
<b>Other conditions of brain</b>				
<b>348.8</b>				
Other conditions of brain	1	6	6	6
XLHED or genetic mutation unknown	1	6	6	6
<b>Diseases Of The Respiratory System</b>				
<b>Acute Respiratory Infections</b>				
<b>Acute bronchitis and bronchiolitis</b>				
<b>466.19</b>				
Acute bronchiolitis due to other infectious organisms	1	2	2	2
XLHED or genetic mutation unknown	1	2	2	2
<b>Acute pharyngitis</b>				
<b>462</b>				
Acute pharyngitis	2	8	4	11
XLHED or genetic mutation unknown	2	8	4	11
<b>Acute sinusitis</b>				
<b>461.0</b>				
Acute maxillary sinusitis	1	5	5	5
NEMO/EDAR mutation	1	5	5	5
<b>461.9</b>				
Acute sinusitis, unspecified	1	12	12	12
NEMO/EDAR mutation	1	12	12	12
<b>Acute upper respiratory infections of multiple or unspecified sites</b>				
<b>465.9</b>				
Acute upper respiratory infections of unspecified site	3	7	2	15
XLHED or genetic mutation unknown	1	2	2	2
NEMO/EDAR mutation	2	10	4	15
<b>Chronic Obstructive Pulmonary Disease And Allied Conditions</b>				
<b>Asthma</b>				
<b>493.00</b>				
Extrinsic asthma without mention of status asthmaticus	2	4	2	5
XLHED or genetic mutation unknown	2	4	2	5
<b>493.02</b>				
Extrinsic asthma with acute exacerbation	1	2	2	2
XLHED or genetic mutation unknown	1	2	2	2
<b>493.9</b>				
Asthma, unspecified	1	1	1	1
XLHED or genetic mutation unknown	1	1	1	1
<b>493.90</b>				
Asthma, unspecified type, without mention of status asthmaticus	3	11	4	16
XLHED or genetic mutation unknown	1	4	4	4
NEMO/EDAR mutation	2	15	13	16
<b>493.92</b>				
Asthma, unspecified type, with acute exacerbation	1	3	3	3
XLHED or genetic mutation unknown	1	3	3	3
<b>Bronchiectasis</b>				
<b>494</b>				

Bronchiectasis	1	13	13	13
NEMO/EDAR mutation	1	13	13	13
494.0				
Bronchiectasis without acute exacerbation	1	21	21	21
NEMO/EDAR mutation	1	21	21	21
Chronic airway obstruction not elsewhere classified				
496				
Chronic airway obstruction, not elsewhere classified	1	49	49	49
XLHED or genetic mutation unknown	1	49	49	49
Chronic bronchitis				
491.8				
Other chronic bronchitis	1	13	13	13
NEMO/EDAR mutation	1	13	13	13
491.9				
Unspecified chronic bronchitis	1	14	14	14
NEMO/EDAR mutation	1	14	14	14
Other Diseases Of Respiratory System				
Other diseases of lung				
518.0				
Pulmonary collapse	1	10	10	10
NEMO/EDAR mutation	1	10	10	10
518.3				
Pulmonary eosinophilia	1	13	13	13
NEMO/EDAR mutation	1	13	13	13
518.4				
Acute edema of lung, unspecified	1	22	22	22
NEMO/EDAR mutation	1	22	22	22
518.82				
Other pulmonary insufficiency, not elsewhere classified	2	8	3	13
XLHED or genetic mutation unknown	1	3	3	3
NEMO/EDAR mutation	1	13	13	13
518.89				
Other diseases of lung, not elsewhere classified	3	16	9	25
NEMO/EDAR mutation	3	16	9	25
Pleurisy				
511.9				
Unspecified pleural effusion	1	21	21	21
NEMO/EDAR mutation	1	21	21	21
Other Diseases Of Upper Respiratory Tract				
Allergic rhinitis				
477.2				
Allergic rhinitis, due to animal (cat) (dog) hair and dander	1	5	5	5
XLHED or genetic mutation unknown	1	5	5	5
477.8				
Allergic rhinitis due to other allergen	1	5	5	5
XLHED or genetic mutation unknown	1	5	5	5
477.9				
Allergic rhinitis, cause unspecified	3	11	2	17
XLHED or genetic mutation unknown	2	8	2	13
NEMO/EDAR mutation	1	17	17	17
Chronic disease of tonsils and adenoids				
474.11				
Hypertrophy of tonsils alone	1	13	13	13
NEMO/EDAR mutation	1	13	13	13
474.12				
Hypertrophy of adenoids alone	1	2	2	2
XLHED or genetic mutation unknown	1	2	2	2
Chronic pharyngitis and nasopharyngitis				
472.0				
Chronic rhinitis	1	41	41	41
XLHED or genetic mutation unknown	1	41	41	41
Chronic sinusitis				
473				

Chronic sinusitis	1	5	5	5
NEMO/EDAR mutation	1	5	5	5
<b>473.0</b>				
Chronic maxillary sinusitis	4	18	5	41
XLHED or genetic mutation unknown	2	23	5	41
NEMO/EDAR mutation	2	13	8	17
<b>473.2</b>				
Chronic ethmoidal sinusitis	3	10	5	17
XLHED or genetic mutation unknown	1	5	5	5
NEMO/EDAR mutation	2	13	8	17
<b>473.8</b>				
Other chronic sinusitis	3	23	13	41
XLHED or genetic mutation unknown	1	41	41	41
NEMO/EDAR mutation	2	15	13	16
<b>473.9</b>				
Unspecified sinusitis (chronic)	4	9	6	17
XLHED or genetic mutation unknown	1	6	6	6
NEMO/EDAR mutation	3	10	6	17
Deviated nasal septum				
<b>470</b>				
Deviated nasal septum	1	17	17	17
NEMO/EDAR mutation	1	17	17	17
Other diseases of upper respiratory tract				
<b>478.1</b>				
Other diseases of nasal cavity and sinuses	1	2	2	2
XLHED or genetic mutation unknown	1	2	2	2
<b>478.29</b>				
Other diseases of pharynx or nasopharynx	1	25	25	25
NEMO/EDAR mutation	1	25	25	25
<b>478.30</b>				
Unspecified paralysis of vocal cords	1	2	2	2
XLHED or genetic mutation unknown	1	2	2	2
<b>478.32</b>				
Unilateral complete paralysis of vocal cords	1	2	2	2
XLHED or genetic mutation unknown	1	2	2	2
Peritonsillar abscess				
<b>475</b>				
Peritonsillar abscess	1	13	13	13
NEMO/EDAR mutation	1	13	13	13
<b>Pneumoconioses And Other Lung Diseases Due To External Agents</b>				
Pneumonitis due to solids and liquids				
<b>507.0</b>				
Pneumonitis due to inhalation of food or vomitus	1	2	2	2
XLHED or genetic mutation unknown	1	2	2	2
<b>Pneumonia And Influenza</b>				
Other bacterial pneumonia				
<b>482.2</b>				
Pneumonia due to Hemophilus influenzae [H. influenzae]	1	13	13	13
NEMO/EDAR mutation	1	13	13	13
<b>482.9</b>				
Bacterial pneumonia, unspecified	1	13	13	13
NEMO/EDAR mutation	1	13	13	13
<b>Pneumococcal pneumonia [streptococcus pneumoniae pneumonia]</b>				
<b>481</b>				
Pneumococcal pneumonia [Streptococcus pneumoniae pneumonia]	1	21	21	21
NEMO/EDAR mutation	1	21	21	21
<b>Pneumonia organism unspecified</b>				
<b>486</b>				
Pneumonia, organism unspecified	5	7	2	17
XLHED or genetic mutation unknown	2	5	2	7
NEMO/EDAR mutation	3	9	5	17
<b>Viral pneumonia</b>				
<b>480.8</b>				

Pneumonia due to other virus not elsewhere classified	1	13	13	13
NEMO/EDAR mutation	1	13	13	13
480.9				
Viral pneumonia, unspecified	1	7	7	7
NEMO/EDAR mutation	1	7	7	7
<b>Diseases Of The Skin And Subcutaneous Tissue</b>				
<b>Infections Of Skin And Subcutaneous Tissue</b>				
Cellulitis and abscess of finger and toe				
681.11				
Onychia and paronychia of toe	1	26	26	26
NEMO/EDAR mutation	1	26	26	26
Impetigo				
684				
Impetigo	2	26	3	49
XLHED or genetic mutation unknown	2	26	3	49
Other cellulitis and abscess				
682.1				
Cellulitis and abscess of neck	1	3	3	3
XLHED or genetic mutation unknown	1	3	3	3
682.2				
Cellulitis and abscess of trunk	1	3	3	3
NEMO/EDAR mutation	1	3	3	3
682.6				
Cellulitis and abscess of leg, except foot	2	7	6	8
XLHED or genetic mutation unknown	1	6	6	6
NEMO/EDAR mutation	1	8	8	8
682.7				
Cellulitis and abscess of foot, except toes	1	49	49	49
XLHED or genetic mutation unknown	1	49	49	49
682.9				
Cellulitis and abscess of unspecified sites	3	25	6	48
XLHED or genetic mutation unknown	2	27	6	48
NEMO/EDAR mutation	1	21	21	21
Other local infections of skin and subcutaneous tissue				
686.0				
Pyoderma	1	10	10	10
NEMO/EDAR mutation	1	10	10	10
686.9				
Unspecified local infection of skin and subcutaneous tissue	2	10	3	17
NEMO/EDAR mutation	2	10	3	17
<b>Other Diseases Of Skin And Subcutaneous Tissue</b>				
Chronic ulcer of skin				
707.10				
Ulcer of lower limb, unspecified	1	47	47	47
XLHED or genetic mutation unknown	1	47	47	47
707.14				
Ulcer of heel and midfoot	1	49	49	49
XLHED or genetic mutation unknown	1	49	49	49
Corns and callosities				
700				
Corns and callosities	1	48	48	48
XLHED or genetic mutation unknown	1	48	48	48
Diseases of hair and hair follicles				
704.00				
Alopecia, unspecified	1	7	7	7
XLHED or genetic mutation unknown	1	7	7	7
704.01				
Alopecia areata	1	4	4	4
XLHED or genetic mutation unknown	1	4	4	4
704.09				
Other alopecia	1	6	6	6
XLHED or genetic mutation unknown	1	6	6	6
704.8				

Other specified diseases of hair and hair follicles	1	25	25	25
NEMO/EDAR mutation	1	25	25	25
Diseases of nail				
703.8				
Other specified diseases of nail	1	50	50	50
XLHED or genetic mutation unknown	1	50	50	50
Diseases of sebaceous glands				
706.2				
Sebacous cyst	1	22	22	22
NEMO/EDAR mutation	1	22	22	22
706.3				
Seborrhea	1	25	25	25
NEMO/EDAR mutation	1	25	25	25
706.8				
Other specified diseases of sebaceous glands	1	48	48	48
XLHED or genetic mutation unknown	1	48	48	48
Other disorders of skin and subcutaneous tissue				
709.00				
Dyschromia, unspecified	1	49	49	49
XLHED or genetic mutation unknown	1	49	49	49
709.3				
Degenerative skin disorders	1	47	47	47
XLHED or genetic mutation unknown	1	47	47	47
709.8				
Other specified disorders of skin	1	11	11	11
NEMO/EDAR mutation	1	11	11	11
709.9				
Unspecified disorder of skin and subcutaneous tissue	2	17	8	25
NEMO/EDAR mutation	2	17	8	25
Other hypertrophic and atrophic conditions of skin				
701.0				
Circumscribed scleroderma	1	47	47	47
XLHED or genetic mutation unknown	1	47	47	47
Urticaria				
708.9				
Unspecified urticaria	1	3	3	3
XLHED or genetic mutation unknown	1	3	3	3
Other Inflammatory Conditions Of Skin And Subcutaneous Tissue				
Atopic dermatitis and related conditions				
691.8				
Other atopic dermatitis and related conditions	3	18	2	50
XLHED or genetic mutation unknown	3	18	2	50
Contact dermatitis and other eczema				
692.89				
Contact dermatitis and other eczema due to other specified agents	1	47	47	47
XLHED or genetic mutation unknown	1	47	47	47
692.9				
Contact dermatitis and other eczema, unspecified cause	5	8	1	16
XLHED or genetic mutation unknown	3	2	1	4
NEMO/EDAR mutation	2	16	15	16
Dermatitis due to substances taken internally				
693.0				
Dermatitis due to drugs and medicines taken internally	3	8	1	16
XLHED or genetic mutation unknown	1	1	1	1
NEMO/EDAR mutation	2	11	6	16
693.1				
Dermatitis due to food taken internally	1	5	5	5
XLHED or genetic mutation unknown	1	5	5	5
693.8				
Dermatitis due to other specified substances taken internally	2	6	5	6
XLHED or genetic mutation unknown	2	6	5	6
Erythematous conditions				
695.89				

Other specified erythematous conditions	1	47	47	47
XLHED or genetic mutation unknown	1	47	47	47
695.9				
Unspecified erythematous condition	1	3	3	3
NEMO/EDAR mutation	1	3	3	3
Endocrine, Nutritional And Metabolic Diseases, And Immunity Disorders				
Diseases Of Other Endocrine Glands				
Diabetes mellitus				
250.03				
type I diabetes mellitus [insulin dependent type] [IDDM] [juvenile type], uncontrolled, without mention of complication	1	49	49	49
XLHED or genetic mutation unknown	1	49	49	49
250.60				
Diabetes mellitus type II [non-insulin dependent type] [NIDDM type] [adult-onset type] or unspecified type, not stated as uncontrolled, with neurological manifestations	1	49	49	49
XLHED or genetic mutation unknown	1	49	49	49
250.70				
Diabetes mellitus type II [non-insulin dependent type] [NIDDM type] [adult-onset type] or unspecified type, not stated as uncontrolled, with peripheral circulatory disorders	1	49	49	49
XLHED or genetic mutation unknown	1	49	49	49
250.72				
Diabetes mellitus type II [non-insulin dependent type] [NIDDM type] [adult-onset type] or unspecified type, uncontrolled, with peripheral circulatory disorders	1	49	49	49
XLHED or genetic mutation unknown	1	49	49	49
250.91				
Diabetes mellitus type I [insulin dependent type] [IDDM] [juvenile type], not stated as uncontrolled, with unspecified complication	1	48	48	48
XLHED or genetic mutation unknown	1	48	48	48
Disorders of adrenal glands				
255.0				
Cushing's syndrome	1	9	9	9
NEMO/EDAR mutation	1	9	9	9
255.4				
Corticoadrenal insufficiency	1	4	4	4
NEMO/EDAR mutation	1	4	4	4
255.41				
Glucocorticoid deficiency	1	12	12	12
NEMO/EDAR mutation	1	12	12	12
255.5				
Other adrenal hypofunction	1	6	6	6
NEMO/EDAR mutation	1	6	6	6
255.8				
Other specified disorders of adrenal glands	1	6	6	6
NEMO/EDAR mutation	1	6	6	6
255.9				
Unspecified disorder of adrenal glands	2	17	7	26
NEMO/EDAR mutation	2	17	7	26
Disorders of parathyroid gland				
252.00				
Hyperparathyroidism, unspecified	1	22	22	22
NEMO/EDAR mutation	1	22	22	22
Disorders of the pituitary gland and its hypothalamic control				
253.3				
Pituitary dwarfism	1	5	5	5
NEMO/EDAR mutation	1	5	5	5
253.5				
Diabetes insipidus	1	5	5	5
NEMO/EDAR mutation	1	5	5	5
Disorders Of Thyroid Gland				
Thyrotoxicosis with or without goiter				
242.90				
Thyrotoxicosis without mention of goiter or other cause, and without mention of thyrotoxic crisis or storm	1	24	24	24



NEMO/EDAR mutation	1	24	24	24
<b>Nutritional Deficiencies</b>				
<b>Kwashiorkor</b>				
260				
Kwashiorkor	1	7	7	7
NEMO/EDAR mutation	1	7	7	7
<b>Other and unspecified protein-calorie malnutrition</b>				
263.0				
Malnutrition of moderate degree	3	9	3	13
XLHED or genetic mutation unknown	1	12	12	12
NEMO/EDAR mutation	2	8	3	13
<b>Other nutritional deficiencies</b>				
269.8				
Other nutritional deficiency	1	11	11	11
XLHED or genetic mutation unknown	1	11	11	11
<b>Other Metabolic Disorders And Immunity Disorders</b>				
<b>Disorders involving the immune mechanism</b>				
279				
Disorders involving the immune mechanism	1	5	5	5
NEMO/EDAR mutation	1	5	5	5
279.00				
Hypogammaglobulinemia, unspecified	3	9	3	16
NEMO/EDAR mutation	3	9	3	16
279.03				
Other selective immunoglobulin deficiencies	3	9	4	19
NEMO/EDAR mutation	3	9	4	19
279.05				
Immunodeficiency with increased IgM	1	2	2	2
NEMO/EDAR mutation	1	2	2	2
279.06				
Common variable immunodeficiency	3	12	7	16
NEMO/EDAR mutation	3	12	7	16
279.1				
Deficiency of cell-mediated immunity	1	13	13	13
NEMO/EDAR mutation	1	13	13	13
279.10				
Immunodeficiency with predominant T-cell defect, unspecified	3	11	6	20
NEMO/EDAR mutation	3	11	6	20
279.19				
Other deficiency of cell-mediated immunity	3	14	3	22
NEMO/EDAR mutation	3	14	3	22
279.2				
Combined immunity deficiency	3	11	5	21
NEMO/EDAR mutation	3	11	5	21
279.3				
Unspecified immunity deficiency	3	12	2	18
NEMO/EDAR mutation	3	12	2	18
279.4				
Autoimmune disease, not elsewhere classified	1	4	4	4
NEMO/EDAR mutation	1	4	4	4
279.8				
Other specified disorders involving the immune mechanism	2	11	3	19
NEMO/EDAR mutation	2	11	3	19
279.9				
Unspecified disorder of immune mechanism	2	6	4	7
NEMO/EDAR mutation	2	6	4	7
<b>Disorders of amino-acid transport and metabolism</b>				
270.9				
Unspecified disorder of amino-acid metabolism	1	7	7	7
NEMO/EDAR mutation	1	7	7	7
<b>Disorders of carbohydrate transport and metabolism</b>				
271.3				
Intestinal disaccharidase deficiencies and disaccharide malabsorption	1	13	13	13

NEMO/EDAR mutation	1	13	13	13
Disorders of fluid electrolyte and acid-base balance				
276.3				
Alkalosis	1	2	2	2
XLHED or genetic mutation unknown	1	2	2	2
276.5				
Volume depletion	3	9	2	22
XLHED or genetic mutation unknown	1	2	2	2
NEMO/EDAR mutation	2	13	3	22
276.52				
Hypovolemia	1	26	26	26
NEMO/EDAR mutation	1	26	26	26
276.6				
Fluid overload	1	22	22	22
NEMO/EDAR mutation	1	22	22	22
276.8				
Hypopotassemia	1	3	3	3
NEMO/EDAR mutation	1	3	3	3
276.9				
Electrolyte and fluid disorders not elsewhere classified	2	16	7	25
NEMO/EDAR mutation	2	16	7	25
Disorders of mineral metabolism				
275.3				
Disorders of phosphorus metabolism	1	12	12	12
NEMO/EDAR mutation	1	12	12	12
Disorders of plasma protein metabolism				
273.8				
Other disorders of plasma protein metabolism	1	3	3	3
NEMO/EDAR mutation	1	3	3	3
Other and unspecified disorders of metabolism				
277.81				
Primary carnitine deficiency	1	5	5	5
NEMO/EDAR mutation	1	5	5	5
277.84				
Other secondary carnitine deficiency	1	5	5	5
NEMO/EDAR mutation	1	5	5	5
Infectious And Parasitic Diseases				
Intestinal Infectious Diseases				
Ill-defined intestinal infections				
009.0				
Infectious colitis, enteritis, and gastroenteritis	3	5	2	9
XLHED or genetic mutation unknown	2	3	2	3
NEMO/EDAR mutation	1	9	9	9
009.1				
Colitis, enteritis, and gastroenteritis of presumed infectious origin	1	5	5	5
NEMO/EDAR mutation	1	5	5	5
Intestinal infections due to other organisms				
008.45				
Intestinal infection due to clostridium difficile	3	11	3	25
NEMO/EDAR mutation	3	11	3	25
008.61				
Enteritis due to rotavirus	1	4	4	4
NEMO/EDAR mutation	1	4	4	4
008.69				
Other viral enteritis	1	7	7	7
NEMO/EDAR mutation	1	7	7	7
008.8				
Intestinal infection due to other organism, not elsewhere classified	1	3	3	3
NEMO/EDAR mutation	1	3	3	3
Mycoses				
Candidiasis				
112.0				
Candidiasis of mouth	1	9	9	9

NEMO/EDAR mutation	1	9	9	9
Other mycoses				
117.9				
Other and unspecified mycoses	1	25	25	25
NEMO/EDAR mutation	1	25	25	25
Other Bacterial Diseases				
Bacterial infection in conditions classified elsewhere and of unspecified site				
041.00				
Unspecified Streptococcus infection in conditions classified elsewhere and of unspecified site	1	2	2	2
XLHED or genetic mutation unknown	1	2	2	2
041.09				
Other Streptococcus infection in conditions classified elsewhere and of unspecified site	1	3	3	3
NEMO/EDAR mutation	1	3	3	3
041.11				
Staphylococcus aureus infection in conditions classified elsewhere and of unspecified site	4	12	2	22
XLHED or genetic mutation unknown	1	2	2	2
NEMO/EDAR mutation	3	15	2	22
041.19				
Other Staphylococcus infection in conditions classified elsewhere and of unspecified site	1	3	3	3
NEMO/EDAR mutation	1	3	3	3
041.2				
Pneumococcus infection in conditions classified elsewhere and of unspecified site	2	5	2	7
XLHED or genetic mutation unknown	1	2	2	2
NEMO/EDAR mutation	1	7	7	7
041.5				
Hemophilus influenzae [H. influenzae] infection in conditions classified elsewhere and of unspecified site	2	10	8	12
NEMO/EDAR mutation	2	10	8	12
041.7				
Pseudomonas infection in conditions classified elsewhere and of unspecified site	1	3	3	3
NEMO/EDAR mutation	1	3	3	3
041.8				
Other specified bacterial infections in conditions classified elsewhere and of unspecified site	1	8	8	8
NEMO/EDAR mutation	1	8	8	8
041.81				
Mycoplasma infection in conditions classified elsewhere and of unspecified site	1	25	25	25
NEMO/EDAR mutation	1	25	25	25
041.85				
Other gram-negative organism infection in conditions classified elsewhere and of unspecified site	2	12	2	21
NEMO/EDAR mutation	2	12	2	21
041.89				
Other specified bacterial infection in conditions classified elsewhere and of unspecified site	1	22	22	22
NEMO/EDAR mutation	1	22	22	22
Diseases due to other mycobacteria				
031.0				
Pulmonary diseases due to other mycobacteria	2	17	8	25
NEMO/EDAR mutation	2	17	8	25
031.1				
Cutaneous diseases due to other mycobacteria	1	11	11	11
NEMO/EDAR mutation	1	11	11	11
031.2				
Disseminated mycobacterial Disease	2	21	17	25
NEMO/EDAR mutation	2	21	17	25
031.8				
Other specified mycobacterial diseases	2	15	11	18
NEMO/EDAR mutation	2	15	11	18

031.9				
Unspecified diseases due to mycobacteria	2	17	8	25
NEMO/EDAR mutation	2	17	8	25
Other bacterial diseases				
040				
Other bacterial diseases	1	5	5	5
NEMO/EDAR mutation	1	5	5	5
Septicemia				
038.43				
Septicemia due to pseudomonas	1	3	3	3
NEMO/EDAR mutation	1	3	3	3
Streptococcal sore throat and scarlet fever				
034.0				
Streptococcal sore throat	3	8	6	13
XLHED or genetic mutation unknown	2	10	6	13
NEMO/EDAR mutation	1	6	6	6
Whooping cough				
033.9				
Whooping cough, unspecified organism	1	9	9	9
NEMO/EDAR mutation	1	9	9	9
Other Diseases Due To Viruses And Chlamydiae				
Infectious mononucleosis				
075				
Infectious mononucleosis	1	13	13	13
NEMO/EDAR mutation	1	13	13	13
Other diseases due to viruses and chlamydiae				
078.10				
Viral warts, unspecified	2	9	5	12
NEMO/EDAR mutation	2	9	5	12
078.19				
Other specified viral warts	1	25	25	25
NEMO/EDAR mutation	1	25	25	25
078.5				
Cytomegaloviral disease	1	3	3	3
NEMO/EDAR mutation	1	3	3	3
Viral and chlamydial infection in conditions classified elsewhere and of unspecified site				
079.99				
Unspecified viral infection in conditions classified elsewhere and of unspecified site	2	14	10	18
XLHED or genetic mutation unknown	1	10	10	10
NEMO/EDAR mutation	1	18	18	18
Viral hepatitis				
070.54				
Chronic hepatitis C without mention of hepatic coma	1	19	19	19
NEMO/EDAR mutation	1	19	19	19
Viral Diseases Accompanied By Exanthem				
Chickenpox				
052.9				
Varicella without mention of complication	2	18	10	25
NEMO/EDAR mutation	2	18	10	25
Herpes simplex				
054.2				
Herpetic gingivostomatitis	1	7	7	7
NEMO/EDAR mutation	1	7	7	7
054.73				
Herpes simplex otitis externa	1	7	7	7
NEMO/EDAR mutation	1	7	7	7
Herpes zoster				
053.19				
Herpes zoster with other nervous system complications	1	25	25	25
NEMO/EDAR mutation	1	25	25	25
053.20				
Herpes zoster dermatitis of eyelid	1	25	25	25
NEMO/EDAR mutation	1	25	25	25

053.29				
Herpes zoster with other ophthalmic complications	1	25	25	25
NEMO/EDAR mutation	1	25	25	25
053.79				
Herpes zoster with other specified complications	1	25	25	25
NEMO/EDAR mutation	1	25	25	25
053.9				
Herpes zoster without mention of complication	1	25	25	25
NEMO/EDAR mutation	1	25	25	25
<b>Injury And Poisoning</b>				
<b>Certain Traumatic Complications And Unspecified Injuries</b>				
<b>Injury other and unspecified</b>				
959.01				
Head injury, unspecified	1	6	6	6
XLHED or genetic mutation unknown	1	6	6	6
959.7				
Other and unspecified injury to knee, leg, ankle, and foot	1	10	10	10
NEMO/EDAR mutation	1	10	10	10
<b>Complications Of Surgical And Medical Care, Not Elsewhere Classified</b>				
<b>Complications of medical care not elsewhere classified</b>				
999.31				
Infection due to central venous catheter	1	25	25	25
NEMO/EDAR mutation	1	25	25	25
999.9				
Other and unspecified complications of medical care, not elsewhere classified	1	25	25	25
NEMO/EDAR mutation	1	25	25	25
<b>Complications Of Surgical And Medical Care, Not Elsewhere Classified</b>				
996.1				
Mechanical complication of other vascular device, implant, and graft	1	18	18	18
NEMO/EDAR mutation	1	18	18	18
996.59				
Mechanical complication due to other implant and internal device, not elsewhere classified	1	11	11	11
NEMO/EDAR mutation	1	11	11	11
996.62				
Infection and inflammatory reaction due to other vascular device, implant, and graft	3	12	2	22
NEMO/EDAR mutation	3	12	2	22
996.74				
Other complications due to other vascular device, implant, and graft	1	21	21	21
NEMO/EDAR mutation	1	21	21	21
996.85				
Complications of bone marrow transplant	1	7	7	7
NEMO/EDAR mutation	1	7	7	7
<b>Other complications of procedures not elsewhere classified</b>				
998.12				
Hematoma complicating a procedure	1	22	22	22
NEMO/EDAR mutation	1	22	22	22
<b>Contusion With Intact Skin Surface</b>				
<b>Contusion of lower limb and of other and unspecified sites</b>				
924.11				
Contusion of knee	1	8	8	8
NEMO/EDAR mutation	1	8	8	8
<b>Fracture Of Lower Limb</b>				
<b>Fracture of one or more tarsal and metatarsal bones</b>				
825.25				
Fracture of metatarsal bone(s), closed	1	7	7	7
NEMO/EDAR mutation	1	7	7	7
<b>Fracture of tibia and fibula</b>				
823.00				
Closed fracture of upper end of tibia	1	4	4	4
NEMO/EDAR mutation	1	4	4	4
823.20				
Closed fracture of shaft of tibia	1	5	5	5

NEMO/EDAR mutation	1	5	5	5
823.80				
Closed fracture of unspecified part of tibia	1	5	5	5
NEMO/EDAR mutation	1	5	5	5
Fracture of unspecified bones				
829.0				
Fracture of unspecified bone, closed	1	5	5	5
NEMO/EDAR mutation	1	5	5	5
Fracture Of Spine And Trunk				
Fracture of rib(s) sternum larynx and trachea				
807.01				
Closed fracture of one rib	1	9	9	9
NEMO/EDAR mutation	1	9	9	9
Fracture Of Upper Limb				
Fracture of metacarpal bone(s)				
815.01				
Closed fracture of base of thumb [first] metacarpal	1	8	8	8
NEMO/EDAR mutation	1	8	8	8
815.10				
Open fracture of metacarpal bone(s), site unspecified	1	8	8	8
NEMO/EDAR mutation	1	8	8	8
Fracture of one or more phalanges of hand				
816.00				
Closed fracture of phalanx or phalanges of hand, unspecified	1	8	8	8
NEMO/EDAR mutation	1	8	8	8
816.02				
Closed fracture of distal phalanx or phalanges of hand	1	8	8	8
NEMO/EDAR mutation	1	8	8	8
Late Effects Of Injuries, Poisonings, Toxic Effects, And Other External Causes				
Late effects of other and unspecified external causes				
909.5				
Late effect of adverse effect of drug, medicinal or biological substance	1	12	12	12
NEMO/EDAR mutation	1	12	12	12
Other And Unspecified Effects Of External Causes				
Certain adverse effects not elsewhere classified				
995.0				
Other anaphylactic shock	1	2	2	2
XLHED or genetic mutation unknown	1	2	2	2
995.3				
Allergy, unspecified, not elsewhere classified	2	5	4	5
XLHED or genetic mutation unknown	1	5	5	5
NEMO/EDAR mutation	1	4	4	4
995.6				
Anaphylactic shock due to adverse food reaction	1	2	2	2
XLHED or genetic mutation unknown	1	2	2	2
995.60				
Anaphylactic shock due to unspecified food	2	6	2	10
XLHED or genetic mutation unknown	2	6	2	10
Sprains And Strains Of Joints And Adjacent Muscles				
Sprains and strains of other and unspecified parts of back				
847				
Sprains and strains of other and unspecified parts of back	1	5	5	5
NEMO/EDAR mutation	1	5	5	5
Superficial Injury				
Superficial injury of face neck and scalp except eye				
910.9				
Other and unspecified superficial injury of face, neck, and scalp, infected	1	3	3	3
XLHED or genetic mutation unknown	1	3	3	3
Superficial injury of hip thigh leg and ankle				
916.0				
Abrasion or friction burn of hip, thigh, leg, and ankle, without mention of infection	1	49	49	49
XLHED or genetic mutation unknown	1	49	49	49
Superficial injury of other multiple and unspecified sites				

<b>919.4</b>				
Insect bite, nonvenomous, of other, multiple, and unspecified sites, without mention				
of infection	1	50	50	50
XLHED or genetic mutation unknown	1	50	50	50
<b>Mental Disorders</b>				
<b>Neurotic Disorders, Personality Disorders, And Other Nonpsychotic Mental Disorders</b>				
Acute reaction to stress				
<b>308.3</b>				
Other acute reactions to stress	1	7	7	7
XLHED or genetic mutation unknown	1	7	7	7
Adjustment reaction				
<b>309.81</b>				
Posttraumatic stress disorder	1	12	12	12
XLHED or genetic mutation unknown	1	12	12	12
Anxiety, dissociative and somatoform disorders				
<b>300.00</b>				
Anxiety state, unspecified	1	7	7	7
XLHED or genetic mutation unknown	1	7	7	7
Disturbance of conduct not elsewhere classified				
<b>312.9</b>				
Unspecified disturbance of conduct	1	6	6	6
XLHED or genetic mutation unknown	1	6	6	6
Special symptoms or syndromes not elsewhere classified				
<b>307.9</b>				
Other and unspecified special symptoms or syndromes, not elsewhere classified	1	7	7	7
XLHED or genetic mutation unknown	1	7	7	7
Specific delays in development				
<b>315.31</b>				
Expressive language disorder	1	7	7	7
XLHED or genetic mutation unknown	1	7	7	7
<b>315.32</b>				
Mixed receptive-expressive language disorder	1	7	7	7
XLHED or genetic mutation unknown	1	7	7	7
<b>315.39</b>				
Other developmental speech disorder	1	3	3	3
XLHED or genetic mutation unknown	1	3	3	3
<b>315.4</b>				
Developmental coordination disorder	1	7	7	7
XLHED or genetic mutation unknown	1	7	7	7
<b>315.5</b>				
Mixed development disorder	1	5	5	5
XLHED or genetic mutation unknown	1	5	5	5
<b>315.9</b>				
Unspecified delay in development	3	8	3	12
XLHED or genetic mutation unknown	3	8	3	12
<b>Organic Psychotic Conditions</b>				
Persistent mental disorders due to conditions classified elsewhere				
<b>294.9</b>				
Unspecified persistent mental disorders due to conditions classified elsewhere	2	10	9	11
XLHED or genetic mutation unknown	1	9	9	9
NEMO/EDAR mutation	1	11	11	11
<b>Other Psychoses</b>				
Episodic mood disorders				
<b>296.32</b>				
Major depressive disorder, recurrent episode, moderate degree	1	49	49	49
XLHED or genetic mutation unknown	1	49	49	49
<b>296.33</b>				
Major depressive disorder, recurrent episode, severe degree, without mention of psychotic behavior	1	49	49	49
XLHED or genetic mutation unknown	1	49	49	49
<b>Neoplasms</b>				
<b>Benign Neoplasms</b>				
Benign neoplasm of skin				

216.7				
Benign neoplasm of skin of lower limb, including hip	1	47	47	47
XLHED or genetic mutation unknown	1	47	47	47
216.9				
Benign neoplasm of skin, site unspecified	1	47	47	47
XLHED or genetic mutation unknown	1	47	47	47
Lipoma				
214.9				
Lipoma, unspecified site	1	48	48	48
XLHED or genetic mutation unknown	1	48	48	48
Malignant Neoplasm Of Other And Unspecified Sites				
Malignant neoplasm of other endocrine glands and related structures				
194.0				
Malignant neoplasm of adrenal gland	1	6	6	6
NEMO/EDAR mutation	1	6	6	6
Supplementary Classification Of External Causes Of Injury And Poisoning				
Accidental Falls				
Accidental fall on same level from slipping tripping or stumbling				
E885.9				
Fall from other slipping, tripping, or stumbling	1	5	5	5
NEMO/EDAR mutation	1	5	5	5
Fracture cause unspecified				
E887				
Fracture, cause unspecified	1	4	4	4
NEMO/EDAR mutation	1	4	4	4
Other accidental falls from one level to another				
E884.2				
Accidental fall from chair or bed	1	3	3	3
XLHED or genetic mutation unknown	1	3	3	3
Other and unspecified fall				
E888.9				
Unspecified fall	2	29	8	49
XLHED or genetic mutation unknown	1	49	49	49
NEMO/EDAR mutation	1	8	8	8
Drugs, Medicinal And Biological Substances Causing Adverse Effects In Therapeutic Use				
Antibiotics causing adverse effects in therapeutic use				
E930.0				
Penicillins causing adverse effects in therapeutic use	2	16	6	25
NEMO/EDAR mutation	2	16	6	25
E930.1				
Antifungal antibiotics causing adverse effects in therapeutic use	1	26	26	26
NEMO/EDAR mutation	1	26	26	26
E930.8				
Other specified antibiotics causing adverse effects in therapeutic use	1	16	16	16
NEMO/EDAR mutation	1	16	16	16
E930.9				
Unspecified antibiotic causing adverse effects in therapeutic use	1	25	25	25
NEMO/EDAR mutation	1	25	25	25
Hormones and synthetic substitutes causing adverse effects in therapeutic use				
E932.0				
Adrenal cortical steroids causing adverse effects in therapeutic use	1	5	5	5
NEMO/EDAR mutation	1	5	5	5
Other and unspecified drugs and medicinal substances causing adverse effects in therapeutic use				
E947.9				
Unspecified drug or medicinal substance causing adverse effects in therapeutic use	1	19	19	19
NEMO/EDAR mutation	1	19	19	19
Primarily systemic agents causing adverse effects in therapeutic use				
E933.1				
Antineoplastic and immunosuppressive drugs causing adverse effects in therapeutic use	1	3	3	3
NEMO/EDAR mutation	1	3	3	3
E935.2				



Other opiates and related narcotics causing adverse effects in therapeutic use	1	13	13	13
NEMO/EDAR mutation	1	13	13	13
<b>Other Accidents</b>				
Striking against or struck accidentally by objects or persons				
E917.9				
Other striking against with or without subsequent fall	1	6	6	6
XLHED or genetic mutation unknown	1	6	6	6
Surgical And Medical Procedures As The Cause Of Abnormal Reaction Of Patient Or Later Complication, Without Mention Of Misadventure At The Time Of Procedure				
Other procedures without mention of misadventure at the time of procedure as the cause of abnormal reaction of patient or of later complication				
E879.8				
Other specified procedures as the cause of abnormal reaction of patient, or of later complication, without mention of misadventure at time of procedure	3	11	3	18
NEMO/EDAR mutation	3	11	3	18
Surgical operation and other surgical procedures as the cause of abnormal reaction of patient or of later complication without mention of misadventure at the time of operation				
E878.8				
Other specified surgical operations and procedures causing abnormal patient reaction, or later complication, without mention of misadventure at time of operation	2	15	7	22
NEMO/EDAR mutation	2	15	7	22
<b>Vehicle Accidents, Not Elsewhere Classifiable</b>				
Place of occurrence				
E849.7				
Accidents occurring in residential institution	2	26	25	26
NEMO/EDAR mutation	2	26	25	26
<b>Supplementary Classification Of Factors Influencing Health Status And Contact With Health Services</b>				
<b>Genetics</b>				
Genetic carrier status				
V83.89				
Other genetic carrier status	1	26	26	26
NEMO/EDAR mutation	1	26	26	26
<b>Persons Encountering Health Services For Specific Procedures And Aftercare</b>				
Attention to artificial openings				
V55.1				
Attention to gastrostomy	1	3	3	3
NEMO/EDAR mutation	1	3	3	3
V55.4				
Attention to other artificial opening of digestive tract	1	6	6	6
NEMO/EDAR mutation	1	6	6	6
Encounter for other and unspecified procedures and aftercare				
V58.62				
Encounter for long-term (current) use of antibiotics	1	9	9	9
NEMO/EDAR mutation	1	9	9	9
V58.69				
Encounter for long-term (current) use of other medications	1	7	7	7
NEMO/EDAR mutation	1	7	7	7
V58.81				
Encounter for fitting and adjustment of vascular catheter	3	28	12	49
XLHED or genetic mutation unknown	1	49	49	49
NEMO/EDAR mutation	2	17	12	22
<b>Persons Encountering Health Services In Circumstances Related To Reproduction And Development</b>				
Health supervision of infant or child				
V20.2				
Routine infant or child health check	1	3	3	3
NEMO/EDAR mutation	1	3	3	3
<b>Persons Encountering Health Services In Other Circumstances</b>				
Follow-up examination				
V67.09				
Follow-up examination following other surgery	1	18	18	18
NEMO/EDAR mutation	1	18	18	18

V67.59				
Other follow-up examination	1	4	4	4
NEMO/EDAR mutation	1	4	4	4
Other persons seeking consultation				
V65.3				
Dietary surveillance and counseling	2	17	8	26
NEMO/EDAR mutation	2	17	8	26
V65.40				
Counseling NOS	1	51	51	51
XLHED or genetic mutation unknown	1	51	51	51
Persons With A Condition Influencing Their Health Status				
Artificial opening status				
V44.1				
Gastrostomy status	2	4	2	5
NEMO/EDAR mutation	2	4	2	5
Organ or tissue replaced by transplant				
V42.4				
Bone replaced by transplant	1	7	7	7
NEMO/EDAR mutation	1	7	7	7
V42.81				
Bone marrow replaced by transplant	1	6	6	6
NEMO/EDAR mutation	1	6	6	6
V42.82				
Peripheral stem cells replaced by transplant	1	7	7	7
NEMO/EDAR mutation	1	7	7	7
V42.84				
Intestines replaced by transplant	1	7	7	7
NEMO/EDAR mutation	1	7	7	7
Other postprocedural states				
V45.1				
Postsurgical renal dialysis status	1	22	22	22
NEMO/EDAR mutation	1	22	22	22
V45.11				
Renal dialysis status	1	25	25	25
NEMO/EDAR mutation	1	25	25	25
V45.4				
Postsurgical arthrodesis status	1	18	18	18
NEMO/EDAR mutation	1	18	18	18
V45.79				
Other acquired absence of organ	1	9	9	9
NEMO/EDAR mutation	1	9	9	9
Persons With Potential Health Hazards Related To Communicable Diseases				
Infection with drug-resistant microorganisms				
V09.0				
Infection with microorganisms resistant to penicillins	3	28	13	49
XLHED or genetic mutation unknown	1	49	49	49
NEMO/EDAR mutation	2	18	13	22
Need for prophylactic vaccination and inoculation against bacterial diseases				
V03.82				
Need for prophylactic vaccination against Streptococcus pneumoniae [pneumococcus]	1	6	6	6
NEMO/EDAR mutation	1	6	6	6
Need for prophylactic vaccination and inoculation against certain viral diseases				
V04.0				
Need for prophylactic vaccination and inoculation against poliomyelitis	1	5	5	5
NEMO/EDAR mutation	1	5	5	5
V04.8				
Need for prophylactic vaccination and inoculation against other viral diseases	1	5	5	5
NEMO/EDAR mutation	1	5	5	5
V04.81				
Need for prophylactic vaccination and inoculation against influenza	1	6	6	6
NEMO/EDAR mutation	1	6	6	6
Need for prophylactic vaccination and inoculation against combinations of diseases				

<b>V06.1</b>				
Need for prophylactic vaccination with combined diphtheria-tetanus-pertussis [DTP]				
[DTaP] vaccine	1	5	5	5
NEMO/EDAR mutation	1	5	5	5
<b>Persons With Potential Health Hazards Related To Personal And Family History</b>				
Other personal history presenting hazards to health				
<b>V15.01</b>				
Allergy to peanuts	1	5	5	5
XLHED or genetic mutation unknown	1	5	5	5
<b>V15.02</b>				
Allergy to milk products	1	10	10	10
NEMO/EDAR mutation	1	10	10	10
<b>V15.03</b>				
Allergy to eggs	2	6	5	7
XLHED or genetic mutation unknown	1	5	5	5
NEMO/EDAR mutation	1	7	7	7
<b>V15.05</b>				
Allergy to other foods	1	5	5	5
XLHED or genetic mutation unknown	1	5	5	5
<b>V15.81</b>				
Personal history of noncompliance with medical treatment, presenting hazards to health				
NEMO/EDAR mutation	2	24	22	26
Personal history of allergy to medicinal agents				
<b>V14.0</b>				
Personal history of allergy to penicillin				
NEMO/EDAR mutation	2	16	7	25
<b>V14.1</b>				
Personal history of allergy to other antibiotic agent				
NEMO/EDAR mutation	1	7	7	7
<b>V14.3</b>				
Personal history of allergy to other anti-infective agent				
NEMO/EDAR mutation	1	7	7	7
<b>V14.8</b>				
Personal history of allergy to other specified medicinal agents				
NEMO/EDAR mutation	1	11	11	11
Personal history of certain other diseases				
<b>V12.61</b>				
Pneumonia (recurrent)				
NEMO/EDAR mutation	1	11	11	11
<b>V12.79</b>				
Other personal history of diseases of digestive system				
NEMO/EDAR mutation	1	8	8	8
<b>Persons Without Reported Diagnosis Encountered During Examination And Investigation Of Individuals And Populations</b>				
General medical examination				
<b>V70.0</b>				
Routine general medical examination at a health care facility				
NEMO/EDAR mutation	1	6	6	6
<b>V70.7</b>				
Examination of participant in clinical trial for normal comparison or control in clinical research				
NEMO/EDAR mutation	1	6	6	6
Observation and evaluation for suspected conditions not found				
<b>V71.8</b>				
Observation and evaluation for other specified suspected conditions				
XLHED or genetic mutation unknown	2	13	4	22
NEMO/EDAR mutation	1	4	4	4
<b>V71.89</b>				
Observation for other specified suspected conditions				
XLHED or genetic mutation unknown	1	4	1	6
NEMO/EDAR mutation	1	1	1	1
Special investigations and examinations				

V72.2				
Special investigations and examinations - Dental examination	1	12	12	12
NEMO/EDAR mutation	1	12	12	12
V72.6				
Laboratory examination	4	14	3	25
XLHED or genetic mutation unknown	1	3	3	3
NEMO/EDAR mutation	3	18	6	25
V72.82				
Preoperative respiratory examination	4	8	3	17
XLHED or genetic mutation unknown	2	5	3	6
NEMO/EDAR mutation	2	12	6	17
V72.83				
Other specified preoperative examination	3	11	2	16
XLHED or genetic mutation unknown	1	2	2	2
NEMO/EDAR mutation	2	16	16	16
Special screening for endocrine nutritional metabolic and immunity disorders				
V77.99				
Screening for other and unspecified endocrine, nutritional, metabolic, and immunity disorders	1	7	7	7
NEMO/EDAR mutation	1	7	7	7
Symptoms, Signs, And Ill-Defined Conditions				
Nonspecific Abnormal Findings				
Nonspecific abnormal findings in other body substances				
792.4				
Nonspecific abnormal findings in saliva	1	13	13	13
NEMO/EDAR mutation	1	13	13	13
Nonspecific abnormal results of function studies				
794.31				
Nonspecific abnormal electrocardiogram [ECG] [EKG]	1	25	25	25
NEMO/EDAR mutation	1	25	25	25
Nonspecific findings on examination of blood				
790.09				
Other abnormality of red blood cells	1	3	3	3
NEMO/EDAR mutation	1	3	3	3
790.1				
Elevated sedimentation rate	1	4	4	4
NEMO/EDAR mutation	1	4	4	4
790.2				
Abnormal glucose	1	19	19	19
NEMO/EDAR mutation	1	19	19	19
790.22				
Impaired glucose tolerance test (oral)	1	22	22	22
NEMO/EDAR mutation	1	22	22	22
790.4				
Nonspecific elevation of levels of transaminase or lactic acid dehydrogenase [LDH]	1	26	26	26
NEMO/EDAR mutation	1	26	26	26
790.7				
Unspecified bacteremia	3	8	2	21
XLHED or genetic mutation unknown	1	2	2	2
NEMO/EDAR mutation	2	12	2	21
790.92				
Abnormal coagulation profile	1	22	22	22
NEMO/EDAR mutation	1	22	22	22
Other and nonspecific abnormal histological and immunological findings				
795.4				
Other nonspecific abnormal histological findings	1	47	47	47
XLHED or genetic mutation unknown	1	47	47	47
Other nonspecific abnormal findings				
796.4				
Other abnormal clinical findings	1	7	7	7
NEMO/EDAR mutation	1	7	7	7
Symptoms				
General symptoms				

780				
General symptoms	2	4	1	6
XLHED or genetic mutation unknown	1	1	1	1
NEMO/EDAR mutation	1	6	6	6
780.6				
Fever	6	15	1	49
XLHED or genetic mutation unknown	3	17	1	49
NEMO/EDAR mutation	3	12	3	18
780.60				
Fever, unspecified	3	21	11	26
NEMO/EDAR mutation	3	21	11	26
780.9				
Other general symptoms	2	32	6	57
XLHED or genetic mutation unknown	1	57	57	57
NEMO/EDAR mutation	1	6	6	6
780.96				
Generalized pain	1	26	26	26
NEMO/EDAR mutation	1	26	26	26
780.99				
Other general symptoms	2	24	21	27
NEMO/EDAR mutation	2	24	21	27
Other symptoms involving abdomen and pelvis				
789.00				
Abdominal pain, unspecified site	3	13	3	21
NEMO/EDAR mutation	3	13	3	21
789.09				
Abdominal pain, other specified site; multiple sites	1	26	26	26
NEMO/EDAR mutation	1	26	26	26
789.1				
Hepatomegaly	1	8	8	8
NEMO/EDAR mutation	1	8	8	8
Symptoms concerning nutrition metabolism and development				
783.0				
Anorexia	1	26	26	26
NEMO/EDAR mutation	1	26	26	26
783.2				
Abnormal loss of weight and underweight	1	12	12	12
XLHED or genetic mutation unknown	1	12	12	12
783.21				
Loss of weight	2	15	3	26
NEMO/EDAR mutation	2	15	3	26
783.22				
Underweight	1	26	26	26
NEMO/EDAR mutation	1	26	26	26
783.3				
Feeding difficulties and mismanagement	4	9	2	22
XLHED or genetic mutation unknown	1	2	2	2
NEMO/EDAR mutation	3	11	5	22
783.4				
Lack of expected normal physiological development in childhood	4	5	2	11
XLHED or genetic mutation unknown	3	5	2	11
NEMO/EDAR mutation	1	2	2	2
783.40				
Lack of normal physiological development, unspecified	2	10	8	12
XLHED or genetic mutation unknown	2	10	8	12
783.41				
Failure to thrive	3	5	2	7
XLHED or genetic mutation unknown	1	2	2	2
NEMO/EDAR mutation	2	6	5	7
783.42				
Delayed milestones	2	5	4	6
XLHED or genetic mutation unknown	2	5	4	6
783.43				

Short stature	1	6	6	6
NEMO/EDAR mutation	1	6	6	6
Symptoms involving cardiovascular system				
785.0				
Tachycardia, unspecified	2	15	4	25
NEMO/EDAR mutation	2	15	4	25
785.59				
Other shock without mention of trauma	1	4	4	4
NEMO/EDAR mutation	1	4	4	4
Symptoms involving digestive system				
787.01				
Nausea with vomiting	1	22	22	22
NEMO/EDAR mutation	1	22	22	22
787.02				
Nausea alone	1	26	26	26
NEMO/EDAR mutation	1	26	26	26
787.03				
Vomiting alone	3	10	2	22
XLHED or genetic mutation unknown	1	2	2	2
NEMO/EDAR mutation	2	15	7	22
787.2				
Dysphagia	2	3	2	3
XLHED or genetic mutation unknown	1	2	2	2
NEMO/EDAR mutation	1	3	3	3
787.3				
Flatulence, eructation, and gas pain	1	5	5	5
NEMO/EDAR mutation	1	5	5	5
787.91				
Diarrhea	2	3	2	3
XLHED or genetic mutation unknown	1	2	2	2
NEMO/EDAR mutation	1	3	3	3
Symptoms involving head and neck				
784.0				
Headache	2	20	13	26
XLHED or genetic mutation unknown	1	13	13	13
NEMO/EDAR mutation	1	26	26	26
784.60				
Symbolic dysfunction, unspecified	1	7	7	7
XLHED or genetic mutation unknown	1	7	7	7
Symptoms involving nervous and musculoskeletal systems				
781.2				
Abnormality of gait	1	4	4	4
NEMO/EDAR mutation	1	4	4	4
781.3				
Lack of coordination	1	2	2	2
XLHED or genetic mutation unknown	1	2	2	2
Symptoms involving respiratory system and other chest symptoms				
786				
Symptoms involving respiratory system and other chest symptoms	1	6	6	6
NEMO/EDAR mutation	1	6	6	6
786.09				
Other dyspnea and respiratory abnormality	3	8	2	13
XLHED or genetic mutation unknown	1	2	2	2
NEMO/EDAR mutation	2	11	9	13
786.2				
Cough	2	9	7	10
NEMO/EDAR mutation	2	9	7	10
786.50				
Unspecified chest pain	1	13	13	13
NEMO/EDAR mutation	1	13	13	13
786.59				
Other chest pain	1	25	25	25
NEMO/EDAR mutation	1	25	25	25

Symptoms involving skin and other integumentary tissue				
<b>782.1</b>				
Rash and other nonspecific skin eruption	3	10	3	22
XLHED or genetic mutation unknown	1	6	6	6
NEMO/EDAR mutation	2	13	3	22
<b>782.8</b>				
Changes in skin texture	1	8	8	8
NEMO/EDAR mutation	1	8	8	8
<b>782.9</b>				
Other symptoms involving skin and integumentary tissues	1	11	11	11
XLHED or genetic mutation unknown	1	11	11	11

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