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Draft Report

Rapid Data Analysis – Hypereosinophilic syndrome in children

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Background	
Short title of topic	Prevalence of hypereosinophilic syndrome (HES) in the paediatric population in EU.
Regulatory procedure	[redacted]
Background	The applicant for a product [redacted] with an intended indication for use in patients with hypereosinophilic syndrome claims in the paediatric investigation plan (PIP) that studies in children younger than 6 years of age are not feasible due to the condition being too rare in this age group. Also, the applicant had included only 4 patients in the age group 6-11 years.

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Background	
	Given the sparse information available in the literature regarding the prevalence of this conditions in children, additional data could be beneficial and better inform the feasibility of current and future clinical trials in children below the age of 12 years with hypereosinophilic syndrome.
Description of research question	What is the yearly prevalence of hypereosinophilic syndrome in children 0-5 and 6-11 years of age in Europe?

1. List of abbreviations

MAH	*Marketing Authorisation Holder*
EMA	*European Medicines Agency*
PDCO	*Paediatric Committee*
PIP	*Paediatric Investigation Plan*
PRAC	*Pharmacovigilance Risk Assessment Committee*
RDA	*Rapid Data Analysis*

2. Amendments and updates

3. Milestones

Milestone	**Planned date**
Analysis proposal	29 November 2021
Feedback on proposal	1 December 2021
Draft results	8 December 2021
Analysis report by	10 December 2021
Registration in the EU PAS register (including study report)	17 December 2021

4. Rationale and background

HES is a constitutes a rare and heterogeneous group of disorders, defined as persistent and marked blood eosinophilia and/or tissue eosinophilia associated with a wide range of clinical manifestations reflecting eosinophil-induced tissue/organ damage [1].

There is only limited information in the literature regarding the prevalence of this conditions in children and clarification of this would help inform the feasibility of current and future clinical trials.

According to data from the World Health Organization from between 2001-2005, the age-adjusted incidence of HES was about 3.6 per 10 million people [2], although this estimate was for myeloproliferative HES [1] and was assessed to translate into an incidence rate for all HES of between 1.8-3.6 per million person-years. The estimated prevalence of HES ranges according to the reference, from 3-63 per million people [1], and another estimate ranges from 10-90 per million people [3]. For myeloproliferative HES the median age at diagnosis was 52.5 years, and rates increased with age to a peak between 65 and 74 years.

Three criteria have traditionally been used to define HES: 1) blood eosinophilia ≥1500/microL for longer than 6 months, 2) lack of evidence for parasitic, allergic or other known causes of eosinophilia, and 3) signs of organ involvement such as heart failure, gastrointestinal dysfunction, central nervous system abnormalities, fever or weight loss [2, 4-7].

After exclusion of known causes (secondary causes), in order to classify the type of HES, patients need to be screened for mutations/gene rearrangements. Patients also need to be screened for clonal or molecular abnormality or increased bone marrow blasts. If these are also not found, patients are screened for abnormal T-cell immune phenotype or Th2 cytokine production.

Depending on the results of these investigations, patients with HES can be categorised as [2]:

- Myeloid/lymphoid neoplasm with eosinophilia and gene rearrangement (e.g. FIP1L1-PDGFRA gene fusion)
- Chronic eosinophilic laeukemia, not otherwise specified (no gene rearrangement but evidence of clonal or molecular abnormality or increased bone marrow blasts)
- Lymphocyte-variant HES (none of the above, but evidence of abnormal T-cell immune phenotype or Th2 cytokine production)
- Idiopathic HES (none of the above)

According to [6], it may be sufficient to document unexplained eosinophilia on more than one occasion, using clinical judgement about the interval and excluding secondary aetiologies, to identify cases of HES.

5. Research question and objectives

The objective of this study was to inform the committee decision making on whether a study in children with HES is feasible in principle, based on reported frequency.

To fulfil this objective the study aimed to estimate the yearly number of newly diagnosed, and the yearly prevalence of HES in children by age group: 0-5 years and 6-11 years. Any cases with a diagnosis of chronic eosinophilic leukaemia would be presented separately.

6. Research methods

6.1. Study design

This was a descriptive study where children 0-11 years of age with possible HES were identified between January 2010 and June 2021. The yearly number of children, and the yearly prevalence of HES was calculated. Results are presented separately for the age groups 0-5 years and 6-11 years.

6.2. Setting

The study was carried out in the IMS® Disease Analyzer France and Germany databases. IMS® Disease Analyzer France contains data from GP practices, and IMS® Disease Analyzer Germany contains data from GP and specialist practices. GP practices in France and GP and paediatric practices in Germany were included in the study

6.3. Variables

6.3.1. HES diagnosis

A diagnosis of HES was based on

- At least one diagnosis of chronic eosinophilic leukaemia (ICD 10 code D47.5) or
- At least two diagnoses of eosinophilia (ICD 10 code D72.1) within a period of 6 months starting at the time of the first diagnosis. The first eosinophilia diagnosis and the last eosinophilia diagnosis during the 6-month period had to be at least one month apart.

'Possible' HES diagnosis was defined as i) all diagnoses of HES identified as described above and ii) not finding a diagnosis for secondary causes (see below section 6.3.2).

'Confirmed' HES was a subset of cases with 'possible' HES diagnosis, requiring in patients with eosinophilia (ICD 10 code D72.1) a note in the diagnosis free-text field confirming that the patient had hypereosinophilia (the option to search in the diagnosis free-text field was only available in IMS® Disease Analyzer Germany).

'Confirmed' HES due to chronic eosinophilic leukaemia would be presented separately.

6.3.2. Exclusion of secondary causes of eosinophilia

Patient with a history of conditions that may cause eosinophilia were excluded. Due to the possibility that patients are investigated for secondary causes after the first eosinophilia diagnosis, a time window of up to 30 days after the first HES diagnosis was considered. The time window prior to the first HES diagnosis depended on the condition to be excluded, please see Table below.

Exclusion conditions	Time window prior to first HES diagnosis	WHO ICD 10 codes
HIV infection	Anytime prior	B20-B24
Primary immunodeficiency disease (hyper-IgE syndrome, Omenn's syndrome)	Anytime prior	D81.8, D82.4
Graft-versus host disease	Anytime prior	T86.0
Sickle-cell disease	Anytime prior	D57
Malignant neoplasms	5 years	C00-C97
Hypoadrenalism	365 days	E27.1- E27.4
Allergic asthma	365 days	J.45.0
Atopic dermatitis	365 days	L20
Eosinophilic pneumonia	365 days	J82
Endomyocardial eosinophilic disease	365 days	I42.3
Eosinophilic cellulitis	365 days	L98.3
Non-infective inflammatory bowel disease	365 days	K50-K52
Inflammatory polyarthropathies	365 days	M05-M14
Systemic connective tissue disorders[1]	365 days	M30-M36
Sarcoidosis	365 days	D86
Esophagitis[2]	365 days	K20
Parasitic disease	90 days	B50-B83
Fungal infections (coccidioidomycosis, aspergillosis)	90 days	B38, B44, J67.0
Scabies	90 days	B86
Myiasis	90 days	B87
Unspecified adverse reaction to drug or medicament	90 days	T88.7

[1]Such as Lupus erythematosus or Sjogren syndrome but not only
[2] Chosen as a proxy for eosinophilic esophagitis

6.4. Data sources and management

The IMS® Disease Analyzer France and Germany databases were used for this study. Version June 2021 of the two databases was used for the analysis. For information about the databases, please see Annex 1.

6.5. Study size

Children 0-11 years during the study period were included in the study.

6.6. Data management

Analyses was carried out using the IHD platform.

6.7. Statistical methods

Patients were considered observable between their first and their last visit to the practice. Age was calculated for each year during the study period. All children aged 0-11 years with at least one day of observability during the year were included in the yearly prevalence calculation. The age groups 0-5 years and 6-11 years were considered separately.

The number of patients with possible HES, and of patients with confirmed HES was provided, cumulatively and per year.

Children 0-11 years diagnosed with HES either during the year or earlier were considered to have HES during the year. The number of children that were diagnosed with HES during the year were provided separately.

The number of children with HES was expressed as a fraction per million children observed during the year.

6.8. Quality control

The quality of IMS® Disease Analyzer data is ensured by a series of continuous quality assurance controls and data refinement at the data provider level (IQVIA). These include checking incoming data for criteria such as completeness and correctness, (e.g. linkage between diagnoses and prescriptions), and standardizing certain data values such as laboratory test results in order to enable reliable analysis.

7. Results

7.1. Descriptive data

7.1.1. IMS® Disease Analyzer France

The yearly number of children 0-11 years observable in the database between 2010 and 2020 varied between 65,885 and 128,953 (during 2021 data was only available until June with a total of 50,244 children observed). Less than 20 children fulfilled criteria for a possible HES diagnosis, all in the 6-11 years category, please see Table 1.

7.1.2. IMS® Disease Analyzer Germany

The yearly number of children 0-11 years observable in the database between 2010 and 2020 varied between 427,127 and 713,890 (during 2021 a total of 343,890 children were observed). A total of 6 children 0-5 years and 51 children 6-11 years fulfilled criteria for a possible HES diagnosis, please see Tables 2 and 3. Only one child, 6-11 years, had a confirmed HES diagnosis diagnosed in 2020. This was based on finding hypereosinophilia in the free text field for eosinophilia. No child was identified with a confirmed diagnosis of chronic eosinophilic leukaemia.

Table 1 Yearly number of children and yearly cases with possible HES in children 0-5 years s IMS® Disease Analyzer France

Year	Total no. of children 0-5 years	No. of children with possible HES diagnosis [1] before exclusion of secondary causes
2010	33,461	0
2011	36,380	0
2012	40,984	0
2013	47,616	0
2014	56,276	0
2015	61,937	0
2016	64,714	0
2017	64,241	0
2018	62,708	0
2019	60,505	0
2020	47,275	0
2021	27,831	0

GVHD = graft versus host disease, HES = hypereosinophilia syndrome, HIV = human immunodeficiency virus,

[1] During the year or earlier.

Counts less than 20 need to be masked for privacy reasons

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Table 2 Yearly number of children and yearly cases with possible HES in children 6-11 years s IMS® Disease Analyzer France

Year	Total no. of children 6-11 years	Number of children with possible HES diagnosis [1] before exclusion of secondary causes	Exclusion for HIV, primary immuno-deficiency, GVHD, sickle-cell disease	Exclusion for malignant neoplasms	Exclusion for eosinophilic inflammatory disease [2]	Exclusion for parasitic or fungal disease or unspecified adverse reaction	Total no. of children with possible HES (diagnosed during the year)
2010	32,424	0	0	0	0	0	0
2011	35,163	0	0	0	0	0	0
2012	38,982	<20	0	0	0	0	<20
2013	44,857	<20	0	0	0	0	<20 (0)
2014	52,845	<20	0	0	<20	0	<20 (0)
2015	59,365	<20	0	0	<20	0	<20 (0)
2016	64,239	<20	0	0	<20	0	0
2017	64,356	<20	0	0	<20	0	0
2018	63,542	<20	0	0	<20	0	0
2019	60,654	<20	0	0	<20	0	<20
2020	48,239	<20	0	0	0	0	<20 (0)
2021	22,413	<20	0	0	0	0	<20 (0)

GVHD = graft versus host disease, HES = hypereosinophilia syndrome, HIV = human immunodeficiency virus,

[1] During the year or earlier.

[2] Hypoadrenalism, allergic asthma, atopic dermatitis, eosinophilic pneumonia, endomyocardial eosinophilic disease, eosinophilic cellulitis, non-infective inflammatory bowel disease, inflammatory polyarthropathies, systemic connective tissue disorders, sarcoidosis and oesophagitis.

Counts less than 20 need to be masked for privacy reasons

Table 3 Yearly number of children and yearly cases with possible HES in children 0-5 years in IMS® Disease Analyzer Germany

Year	Total no. of children 0-5 years	No. of with possible HES diagnosis [1] before exclusion of secondary causes [1]	Exclusion for HIV, primary immuno-deficiency, GVHD, sickle-cell disease	Exclusion for malignant neoplasms	Exclusion for eosinophilic inflammatory disease [2]	Exclusion for parasitic or fungal disease or unspecified adverse reaction	Total no. of children 0-5 years with possible HES (diagnosed during the year)
2010	223,149	4	0	0	2	2	0
2011	255,831	6	0	0	2	3	1 (1)
2012	281,623	4	0	0	1	2	1 (0)
2013	305,454	4	0	0	2	2	0
2014	321,807	9	0	0	3	4	2 (2)
2015	331,039	8	0	0	3	4	1 (1)
2016	374,223	8	0	0	3	4	1 (0)
2017	388,337	8	0	0	3	3	2 (1)
2018	386,341	10	0	0	4	4	2 (1)
2019	378,665	7	0	0	5	1	1 (0)
2020	327,040	5	0	0	5	0	0
2021	188,226	1	0	0	1	0	0

GVHD = graft versus host disease, HES = hypereosinophilia syndrome, HIV = human immunodeficiency virus,

[1] During the year or earlier.

[2] Hypoadrenalism, allergic asthma, atopic dermatitis, eosinophilic pneumonia, endomyocardial eosinophilic disease, eosinophilic cellulitis, non-infective inflammatory bowel disease, inflammatory polyarthropathies, systemic connective tissue disorders, sarcoidosis and oesophagitis.

Table 4 Yearly number of children and yearly cases with possible HES in children 6-11 years in IMS® Disease Analyzer Germany

Year	Total no. of children 6-11 years	No. of children 6-11 years evaluated for a possible HES diagnosis [1]	Exclusion for HIV, primary immuno-deficiency, GVHD, sickle-cell disease	Exclusion for malignant neoplasms	Exclusion for eosinophilic inflammatory disease [2]	Exclusion for parasitic or fungal disease or unspecified adverse reaction	Total no. of children 6-11 years with possible HES (diagnosed during the year) [3]
2010	203,978	6	0	0	3	1	2 (2)
2011	234,943	12	0	0	2	2	8 (7)
2012	252,719	13	0	0	3	3	7 (2)
2013	272,618	18	0	0	4	6	8 (1)
2014	282,783	20	0	0	4	7	9 (4)
2015	288,602	17	0	0	4	7	6 (2)
2016	317,195	20	0	0	4	7	9 (5)
2017	325,553	25	0	0	5	7	13 (5)
2018	324,143	25	0	0	2	4	19 (7)
2019	308,153	28	0	0	1	4	23 (7)
2020	266,970	22	0	1	1	3	17 (3)
2021	155,664	17	0	1	3	2	11 (3)

GVHD = graft versus host disease, HES = hypereosinophilia syndrome, HIV = human immunodeficiency virus,

[1] During the year or earlier.

[2] Hypoadrenalism, allergic asthma, atopic dermatitis, eosinophilic pneumonia, endomyocardial eosinophilic disease, eosinophilic cellulitis, non-infective inflammatory bowel disease, inflammatory polyarthropathies, systemic connective tissue disorders, sarcoidosis and oesophagitis.

[3] Three of the children had been diagnosed with HES between age 0-5 years.

7.2. Yearly prevalence of HES

The prevalence of HES per million children observed during the year is shown in Table 5 for IMS® Disease Analyzer France and in Table 6 for IMS® Disease Analyzer Germany. The prevalence for possible HES appears to be lower in children 0-5 years of age compared to children 6-11 years of age, although no statistical comparison was performed. No case of confirmed HES was identified in children 0-5 years of age.

Table 5 Prevalence of possible and probable HES per million children 0-5 years and 6-11 years of age in IMS® Disease Analyzer France

Prevalence of possible HES		
Year	Children 0-5 years	Children 6-11 years
2010	0.0 (0.0-89.7)	0.0 (0.0-92.5)
2011	0.0 (0.0-82.5)	0.0 (0.0-85.3)
2012	0.0 (0.0-73.2)	51.3 (50.9-51.7)
2013	0.0 (0.0-63.0)	22.3 (22.1-22.5)
2014	0.0 (0.0-53.3)	18.9 (18.8-19.1)
2015	0.0 (0.0-48.4)	16.8 (16.7-17.0)
2016	0.0 (0.0-46.4)	0.0 (0.0-46.7)
2017	0.0 (0.0-46.7)	0.0 (0.0-46.6)
2018	0.0 (0.0-47.8)	0.0 (0.0-47.2)
2019	0.0 (0.0-49.6)	16.5 (16.4-16.6)
2020	0.0 (0.0-63.5)	20.7 (20.5-20.9)

CI = confidence interval. For 0 events, the rule of 3 has been used to calculate the upper confidence limit

Table 6 Prevalence of possible and probable HES per million children 0-5 years and 6-11 years of age in IMS® Disease Analyzer Germany

Prevalence possible HES		
Year	Children 0-5 years	Children 6-11 years
2010	0.0 (0.0-13.4)	9.8 (9.8-9.8)
2011	3.9 (3.9-3.9)	34.1 (34.0-34.1)
2012	3.6 (3.5-3.6)	27.7 (27.7-27.7)
2013	0.0 (0.0-9.8)	29.3 (29.3-29.4)
2014	6.2 (6.2-6.2)	31.8 (31.8-31.9)
2015	3.0 (3.0-3.0)	20.8 (20.8-20.8)
2016	2.7 (2.7-2.7)	28.4 (28.3-28.4)
2017	5.2 (5.1-5.2)	39.9 (39.9-40.0)
2018	5.2 (5.2-5.2)	58.6 (58.6-58.7)
2019	2.6 (2.6-2.6)	74.6 (74.6-74.7)
2020	0.0 (0.0-9.2)	63.7 (63.6-63.7)

CI = confidence interval. For 0 events, the rule of 3 has been used to calculate the upper confidence limit.

8. Discussion

This study was carried out to identify children 0-11 years with possible HES and to estimate the prevalence in primary care databases in France and Germany.

Cases identified based on a diagnosis of eosinophilia were initially considered as possible HES whereas cases identified based on chronic eosinophilic leukaemia were considered as confirmed HES. For IMS Germany only, cases with possible HES could subsequently be confirmed if hypereosinophilia was mentioned in the free text field for the diagnosis.

Results of this study showed that cases with possible HES were rare in children 0-5 years with an estimated yearly prevalence between 0.0 and 6.2 per million children, and no child 0-5 years had a confirmed HES diagnosis. Possible HES was somewhat less rare in children 6-11 years with an estimated yearly prevalence between 0.0 and 74.6, and a single child was identified with confirmed HES.

These results were based on a paediatric population of around 30,000-60,000 children per age group per year in France and around 200,000-380,000 children per age group per year in Germany.

This study was carried out using electronic health records from primary care. The extent to which HES might be diagnosed in primary care is not known. It seems likely that patients with HES are referred to secondary care for specific testing to be able to confirm the diagnosis. Even if a diagnosis made in secondary care can subsequently be recorded also in primary care, the counts shown might be underestimated.

The lack of a specific diagnosis code (WHO ICD 10 code) for HES and the absence of data on specific testing for HES (e.g. tests for gene rearrangement) were important limitations of the study (for a more detailed discussion on the limitation, please see section 9).

The most important limitations concern the lack of eosinophil values to be able to establish the level of eosinophilia, which reduced our ability to confirm cases of HES, and might lead to misclassification of some transitory eosinophilia cases as HES, and therefore cases defined as 'possible HES' might overestimate HES.

On the other hand, for confirmed HES we required either a diagnosis of chronic eosinophil leukaemia or a note in the free text field for the diagnosis that the patient had hypereosinophilia. One such case was identified in the study, based on identifying hypereosinophilia in the free text field for eosinophilia, and it is possible that confirmed cases were under-diagnosed as the physician might not have made a note of hypereosinophilia in all cases fulfilling the definition for HES. Cases defined as 'confirmed HES' might therefore underestimate HES. No child was identified with a diagnosis of chronic eosinophilic leukaemia.

In addition, the population was estimated from children visiting health care, and not from all children in the population, which could lead to overestimation of the prevalence.

9. Conclusion

Published literature has suggested that the prevalence of HES (in the whole population) could be between 3-90 per million people [1, 3]. Prevalence is expected to be at the lower end of this range in children considering that the incidence rate has been shown to increase with increasing age. Results of this study are consistent with the lower end of the estimates of the published literature, especially the data on confirmed HES, where we could only identify a single child based on the recording of hypereosinophilia in the free text field across all study years. The data on cases with possible HES is more difficult to interpret as we cannot be confident about the relationship between a possible HES diagnosis and a confirmed HES diagnosis.

Of note that this study was performed in two European countries with databases with information from primary care; the availability of data sources from additional European countries covering also specialised care will help overcoming some of the limitations identified.

9. References

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10. Annex 1 Characteristics of the healthcare systems and the included databases

France

Primary care in France includes GPs and specialists. Patients have free physician choice. Registration with a GP is not required but patients are asked to register with a preferred doctor of their choice (médecin traitant) who can be a GP or a non-GP. This doctor should be visited before accessing another doctor, and patients with a referral pay less for visits and prescriptions. However, a referral is not required for gynaecologists, ophthalmologists and psychiatrists.

The physician is not required to provide a diagnosis, and may be less likely to record a repeated diagnosis in patients with persistent conditions compared to the first occasion of the diagnosis.

IMS® Disease Analyzer France collects anonymised patient medical records since 1997 through a representative panel of GPs. The physician sample represents approximately 2 % of physicians, and is weighted by age and gender of the physician, doctor region and the SNIR of the physician (National Official Indicator of the GP volume of activity in terms of visits and consultations) [10]. The age distribution of patients has been shown to be similar to France social security data (SNIIRAM).

Germany

Primary care in Germany includes GPs and specialists. Patients have free physician choice. Registration with a GP is not required, and specialists can be consulted without a referral from a GP. In Germany there are some disease programs where patients are followed more closely, e.g. diabetes.

The physician is required to provide a diagnosis, and also to provide their judgement on the diagnosis using the following categories: 1) confirmed current diagnosis, 2) suspected current diagnosis, 3) excluded current diagnosis, 4) confirmed non-current diagnosis, and 5) unspecified.

IMS® Disease Analyzer Germany collects computerised information from specialised and general primary care practices throughout Germany since 1992. Around 3% of GP practices are included in IMS® Disease Analyzer Germany from the different regions in Germany. Data from IMS® Disease Analyzer Germany have been shown to be reasonably representative of German healthcare statistics for demographics and certain diseases [8, 9]. This study will include all practices prescribing the antibiotics of interest and will not be restricted to GP practices only.

Patients included in the database

The databases only include patients visiting a primary care physician, i.e. healthy individuals not visiting a primary care physician are missing in the database.

A patient has the same ID only within the same practice. If the patient also visits another practice, a new ID is allocated. For this reason it is not possible to follow patients across different healthcare providers and data can therefore be fragmented and incomplete.

Limitations related to the recording of diagnoses

The two databases use WHO ICD codes for the recording of diagnoses, and eosinophil counts are not available. There is no specific WHO ICD code for hypereosinophilia except for D47.5 (chronic

eosinophilic leukemia), which is a subtype of HES. It is therefore necessary to use an algorithm based on a diagnosis of eosinophilia to identify patients with possible HES. This may lead to overidentification of HES (which requires eosinophil levels ≥1500/microL) due to inclusion of patients with eosinophil values below 1500/microL.

Similarly, it is possible that there is incomplete recording (also due to limited longitudinal information) of all possible secondary causes of hypereosinophilia, which may lead to overidentification of HES due to failure to remove secondary causes.

A free text field for the diagnosis will be used to identify eosinophilia cases where the physician has noted hypereosinophilia, which may then be regarded as confirmed. However, due to incomplete recording of free texts this may lead to underidentification of HES.

Incomplete patient history due to limited longitudinal information may also impact on the ability to diagnose the condition, especially if a diagnosis was made prior to the first visit of the patient and was not repeated after the patient entered the practice, which would lead to underidentification of HES.

It may be likely that patients are diagnosed in hospital settings as outpatients or inpatients and this study relies on diagnoses being transferred from such secondary care hospital settings to the patient's GP (and paediatrician for IMS Germany). Such transfer of diagnosis may be incomplete, which would lead to underidentification of HES.

11. Comments received on draft analysis plan

Comments received

1. Will this be published (The PIP application background)? I assume not.

2. This list (Table) should include more autoimmune diseases (e.g. Lupus erythematosus or Sjogren syndrome), allergic diseases (eosinophilic esophagitis, enterocolitis) and Gleich's syndrome (or Episodic angioedema with eosinophilia).

EMA Comment

1. The sensitive information has been removed.

2. Lupus and Sjogren are included in 'systemic connective tissue disorders'. There is no specific ICD 10 code for eosinophilic esophagitis, so esophagitis will be excluded. The enterocolitis should be covered by the code for 'non-infective inflammatory bowel disease.' Gleich syndrome does not have a specific ICD 10 code (it is actually included in D72.1 which is our target), please see also https://www.cdc.gov/nchs/data/icd/Topic-packet-March-2019-Part-2Vs3.pdf which includes Gleich syndrome as one of the hypereosinophilic syndromes). Added as a footnote to the table as well.

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