A national epidemiological study of inherited ichthyoses in England from 1998-2024

Mark D Eisner,[1,2,3] Maisie Blyth,[3] Jennifer M Broughan,[3] Corinne Mallinson,[3] Lizz Paley,[3] Jeanette Aston,[3] Sally Vernon,[3] Steven Hardy,[3] Shehnaz Ahmed,[4] Mandy Aldwin-Easton,[5] Shaimaa Lashin,[6] Julia Fordham,[7] Celia Moss,[8,9] Marie-Louise Lovgren,[8,10] Edel A O'Toole,[11] Zoe C Venables[3,12,13] and Neil Rajan[1,2]

1 Translational Clinical Research Institute, Newcastle University, Newcastle, UK

2 Department of Dermatology, Royal Victoria Infirmary, Newcastle, UK

3 National Disease Registration Service, Leeds, UK

4 British Association of Dermatologists, London, UK

5 Ichthyosis Support Group, Wokingham, UK

6 Department of Dermatology, Nottingham University Hospitals NHS Foundation Trust, Nottingham, UK

7 Torbay and South Devon NHS Foundation Trust, Devon, UK

8 Department of Dermatology, Birmingham Women's and Children's Hospitals NHS Foundation Trust, Birmingham, UK

9 University of Birmingham College of Medical and Dental Sciences, Birmingham, UK

10 Queen Elizabeth Hospital, University, Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

11 Centre for Cell Biology and Cutaneous Research, Blizard Institute, Queen Mary University of London, London, UK

12 Norwich Medical School, University of East Anglia, Norwich, UK

13 Norfolk and Norwich University Hospitals NHS Foundation Trust, Norwich, UK

Corresponding author: Neil Rajan

Email: neil.rajan@newcastle.ac.uk

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What is already known about this topic?

- National epidemiological data of the inherited ichthyoses in England, combined with patient level comorbidities and genetic testing status, is lacking.

What does this study add?

- This study uses routinely collected data drawn from the health records of 57 million people in England to establish the prevalence of inherited ichthyoses, their association with systemic comorbidities and genetic testing status.
- There is an increased burden beyond the skin for some patients with ichthyosis for associated asthma, inflammatory arthropathies, and atrial fibrillation.

- Genetic testing data reveals a low rate of tested cases, underscoring the need for improved access to testing to inform recent proposals for dyadic diagnosis of ichthyoses.

Abstract

Background Ichthyoses cause significant morbidity and mortality, however national epidemiological data that link diagnoses of ichthyoses with systemic comorbidities are lacking.

Objective Report epidemiological data on inherited ichthyoses in England, together with patient level comorbidities and genetic testing status.

Methods This national retrospective cohort study identified ichthyosis case records from healthcare databases in England, using ICD-10 codes from 1998-2024. Cohort demographics, comorbidities, genetic testing data, and mortality data were extracted from routinely collected NHS data.

Results We identified 4330 ichthyosis patients, of which 3758 were categorised as having a rare ichthyosis. Prevalence of the rare ichthyoses was 51.6 per million [95% CI 49.7–53.5]. Compared to the reference population, the overall cohort was younger (median age 22 (interquartile range 38) vs. 41 years), more likely to identify as Asian (17.1% vs 9.6%, $P < 0.001$), and more frequently in the most deprived quintiles (48.1% vs 40%, $P < 0.001$). Rates of comorbidities including asthma, inflammatory arthropathies and atrial fibrillation were higher than in the reference population. 18.5% of deaths occurred before 25 years of age compared with 1% of deaths at this age threshold in the reference population ($P < 0.001$). Genetic testing data revealed a low proportion of tested cases; pathogenic variants in genes known to cause ichthyosis were found in 90 (56%) of the 160 tested cases.

Conclusions We report an increased range of comorbidities in patients living with rare ichthyoses, highlighting the systemic burden in patients categorised as having non-syndromic ichthyosis. These data inform healthcare planning, research design and the redressing of inequities of care.

Introduction

The inherited ichthyoses, recently renamed as non-syndromic and syndromic epidermal differentiation disorders (nEDD, sEDD) and referred to as ichthyoses hereinafter,[1–3] are a heterogeneous group of genodermatoses driven by pathogenic variants in single genes affecting epidermal differentiation. People living with rare ichthyoses may have a severe cutaneous phenotype leading to significant morbidity and mortality. It is also now increasingly recognised that even ichthyoses which were thought to be non-syndromic have extracutaneous manifestations; X-linked ichthyosis is now recognised to be associated with atrial fibrillation[4] and neurodevelopmental disorders.[5] Ichthyosis associated comorbidities may hence be under recognised, and has not been systematically studied across rare ichthyoses.

People living with rare ichthyoses frequently report pain, pruritus, poor quality of sleep, discrimination, and social isolation.[6] Depression and anxiety have also been significantly associated,[7] and rare ichthyoses are associated with one of the highest levels of stigma across skin disorders.[8] There are no curative treatments available for ichthyosis,[9,10] and recent studies have shown the potential of repurposed biologics in some patients.[9]

Epidemiological studies of the ichthyoses have been limited, and previous studies focussed on specific ichthyosis subtypes or geographic regions.[11–14] Prior national studies include a Danish prevalence study including 952 patients (160 per million people),[15] and a study of moderate to severe ichthyoses diagnosed in the USA reported an incidence of 67 per million people.[16,17] The largest genotype-phenotype study of an international cohort of 1,000 individuals, established a phenotypic correlation in some subtypes of ichthyoses.[18]

Here, in partnership with the United Kingdom's ichthyosis patient organisation (Ichthyosis Support Group/ISG), we agreed research priorities for a national study that aimed to delineate demographics, associated co-morbidities and provision of genetic testing. To achieve these aims we utilised the National Disease Registration Service (NDRS) which allowed for the interrogation of health records across England to identify patients coded with a diagnosis for ichthyosis. A similar approach had previously been used successfully in rare autoimmune and rheumatological conditions[19,20] in England. These data aim to inform patient resource provision, address inequities as well as improve opportunities for clinical trials and research for people with ichthyosis.

Methods

This national retrospective cohort study conducted within the NDRS, identified cases of ichthyosis from a population of 57,690,323 people. It utilised multiple sources of routinely collected healthcare data in England, described in detail previously.[21–23] Hospital Episode Statistics (HES, January 1998 to April 2024), accessed via the UK Health Security Agency, collects clinical and demographic information primarily for administrative purposes following every inpatient and outpatient encounter[21] and were combined with genetic testing data, routinely collected by the NDRS from Genomic Laboratory Hubs (January 2021 to September 2024). To enhance diagnostic precision and ascertainment coverage, data were integrated from the national congenital condition register collected by National Congenital Anomaly and Rare Disease Registration Service (NCARDRS) for babies born between 2015 and 2021[22] and data from five regional legacy congenital anomaly registers, which registered congenital conditions for some regions from 1980s to 2005. The national and legacy congenital regional registries are distinct from HES in that they contain ichthyosis cases that were actively registered and clinically validated. Cases, identified using International Classification of Diseases 10 (ICD-10) codes (Table S1a), were deduplicated using NHS numbers (the national unique patient identifier for England, which was the primary identifier for linkage across databases). Legacy and NCARDS diagnoses were favoured over HES diagnoses as they are verified by clinicians at time of registration. When multiple competing diagnoses were available for a case, the most frequently recorded, and then the most recently recorded were chosen in case of a tie. Full details are available within the Supplementary Methods.

Deprivation quintiles were derived from national Index of Multiple Deprivation (IMD) data which measures relative deprivation in small areas of up to 1200 households.[24] Regional location of each case was determined using the Office for National Statistics (ONS) National Statistics Postcode Lookup (NSPL).[25] Age at the time of the study (June 2023) and age at death were taken from the Personal Demographics Service (PDS) database and compared to the 2023 reference ONS database for England.[26] Ethnicity proportions were compared to reference English census data.[27] Chi-squared tests were performed when appropriate. Underlying cause of death, as recorded on death certificates, were obtained from the NHS England Data Access Environment (NHSE DAE), where available, and compared to reference population data from 2012-2023.[28] Prescription data were obtained from NHS Business Services Authority *via* the NHSE DAE for the cohort and prescriptions were categorised by British National Formulary chapters. Code used for data extraction was generated and checked according to NDRS policies; all NDRS code is available on GitHub (https://github.com/NHSE-NDRS).

In England, a panel of genes known to cause ichthyosis and erythrokeratoderma (R165) is updated at least every year and forms part of the NHS UK Gene Testing Network

Directory; the current reported genes are in Table S2.[23] The total number of R165 genetic tests performed nationally was captured from NHS Patient Level Contract Monitoring (PLCM) data.[29] Representative patient level genetic test data were available from Great Ormond Street Hospital (GOSH) which is one of two national Genomic Laboratory Hubs.[23] Positive genetic tests were defined as pathogenic or likely pathogenic, all other results were classed as non-diagnostic.[30]

Validation

To assess the accuracy of the diagnostic data, a subset of cases identified at nine hospitals, , excluding those found in previously validated registries, were provided to local clinicians for validation. These clinicians were instructed to review routinely available medical records to verify the diagnosis of ichthyosis and select appropriate corresponding ORPHAnet diagnostic codes (orphacodes.org) which were then converted into ICD-10 codes (Table S3). Of the 337 returned cases, 202 (59.9%) were confirmed to have a form of ichthyosis. Our validation strategy was allowed for 7.8% of all cases to be validated, which is higher than other similar studies which have validated < 0.5% of cases.[19] Subtype confirmation rate varied between 40.5% and 71.2% across the five hospitals providing data (Table S4). Non-validated cases (n=135) were retained in the main analyses.

Results

Patients with ichthyosis were younger compared to the reference population

We identified 4330 people with an ichthyosis in England, of which 3758 were categorised as having rare ichthyoses. The overall cohort was majority male (58.1%) and had a median age 22 years (IQR 38) (Table 1). The largest proportion of rare ichthyosis diagnoses were captured under ICD-10 codes for 'Unspecified congenital' (45.6%), followed by CBIE (12.5%), 'Other congenital' (8.0%) and X-linked (7.5%); IV comprised 13.2%.

A higher proportion of the cohort self-identified as having Asian ancestry compared to the reference population (17.1% vs 9.6%, $P < 0.001$). Specifically, increased enrichment for ichthyoses was seen in people describing their ancestry as Pakistani (Table S5); 9.1% of the cohort had Pakistani ancestry compared to 2.8% of the reference population ($P < 0.001$). Across the different diagnostic codes, this was particularly significant for patients with LI (40.5%, $P < 0.001$) (Figure S1).

Regional variations in the prevalence of ichthyosis across England, and disproportionate representation of deprivation.

The recorded point prevalences, as of June 2023, per million people, were: overall 59.4 [95% confidence interval (CI) 57.5-61.5], rare ichthyoses 51.6 [49.7–53.5] of which: CBIE 6.1 [5.5-6.8], X-linked 5.2 [4.6-5.8], LI 5.0 [4.5-5.7], HI 4 [3.5-4.6], other congenital 5.1 [4.5-5.7] and unspecified congenital 26.1 [24.8-27.4]; IV was recorded as 7.9 [7.1-8.6] (Table 1). The highest prevalences of ichthyoses overall per million people were in the West Midlands (73.5 [66.8-80.6]) and the Northeast (66.8 [57.4-77.2]) (Table 1 and Figure 2). People with ichthyosis were more commonly in the two most deprived quintiles (48.1% vs 40%, $P < 0.001$) (Table 1).

Increased burden of extracutaneous symptoms in people with ichthyosis and increased mortality

We investigated the prevalence of extracutaneous symptoms in people categorised as living with rare ichthyosis in our cohort (n=3758) (Table 2) and their prescription data (Figure S2). 18.8% of the rare ichthyosis cohort had a diagnosis of asthma, which is significantly higher than the reference population (6.5%, $P < 0.001$).[31] The largest group comprised patients with a diagnosis of CBIE (n=541), of which 115/541 (21.3%) had a diagnostic label of asthma. Comparative analysis of the IV cohort revealed 173/572 (30.2%) had a diagnostic label of asthma.

Inflammatory polyarthropathies were reported in 10.3% of the rare cohort's records (n=387), of which rheumatoid arthritis (RA) comprised 159 records (4.2%) (Table 2). RA, for which population prevalences are available, was more frequent in our cohort than in the general population ($P < 0.001$).[31] Atrial fibrillation was recorded in 9.6% (n=362) of the cohort, a significantly higher prevalence than the 2.2% found in the general population ($P < 0.001$).[31] The prevalence was particularly high among patients with CBIE (12.6%, n=68/541), and 'unspecified ichthyosis' (12.6%, n=249/1975).

In the rare ichthyosis cohort, diagnoses of autism or Asperger's syndrome (2.6%; n=96) and cerebral palsy (9.2%; n=344) were significantly ($P < 0.01$) higher than published baselines (1.1%[32] and 3.4%[33], respectively). Conversely, recorded rates within the depression group (10.8%; n=404) and for ADHD (1.3%; n=48) were significantly ($P < 0.01$) lower than the general population reference figures of 13.7%[31] and 4.0%[34]. Patients with X-linked ichthyosis had the highest recorded rates of ADHD (18/325, 5.5%) and autism or Asperger's (17/325, 5.2%). In the overall ichthyosis cohort, 18.5% of deaths occurred before the age of 25; in comparison only 1% of deaths registered in England in 2023 were in this age group ($P < 0.001$).[26] 79.2% of the overall cohort were alive on the 1st of June 2023.

Median age at death for the overall cohort was 74 years (IQR 35). HI and LI subtypes had the lowest median age of death at 0, IQR 32 and 62 respectively (Table 1).

Recorded cause of death according to ONS death certificate data was available for 886 of the 901 deceased patients (Table S6). The two most common recorded causes of death in under 25's (n=167) were: 'cerebral palsy' (14, 8.3%) and 'congenital ichthyosis' (13, 7.8%) (Table S7); the cause of death was not known in 24 (14.4%) cases,

High yield of pathogenic variants in genotyped ichthyosis patients

NHS contracting data revealed 382 tests had been performed nationally between January 2021 and September 2025 indicating a rate of 80 tests per year. Patient level genetic test data were available for 160 patients from January 2021 to September 2024 (Table 3), of these 90 (56%) were found to have pathogenic variants and 37.5% were less than 5 years old at time of testing. The most frequently reported PVs were in *STS,* 16 (18%), *TGM1,* 11 (12%) and *NIPAL4,* 9 (10%). These figures are a representative sampling of national ichthyosis test requests during this period.

Discussion

In this study we curated 3758 patients with rare ichthyoses across England. Our reported prevalence of 51.6 [49.7–53.5] cases per million people is similar to previously published data for the rare ichthyoses (Figure S3).[16,35–37] Strikingly, we found associated comorbidities to be increased across a range of subtypes of rare ichthyoses, considered "non-syndromic", highlighting an unrecognised extracutaneous burden.

We identified inflammatory polyarthropathies in over 10% of the rare ichthyosis cohort, a previously unknown association outside of certain rare subtypes such as HI.[38–40] In these case reports of HI, rare inflammatory arthritides such as Juvenile Idiopathic Arthritis (OMIM 604302) and the subtype Juvenile Rheumatoid Arthritis has been reported in patients with a clinical diagnosis of HI. These arthritides are currently linked to risk loci encoding genes including Interleukin 6 and *MIF*, however are considered rare polygenic traits. In skin, bulk transcriptomic analysis has revealed that the EI, Netherton's and LI can carry an IL-17 immunophenotype detectable in the skin but also in peripheral blood. This systemic inflammation provides a potential biological rationale for our findings in other tissue mirroring the systemic nature of other Th17-mediated diseases such as psoriasis and its link to psoriatic arthritis.[41,42]

In our data there were also high rates of other extracutaneous features. Higher prevalences of asthma than in the general population were not explained by IV alone, and

were also seen in other subtypes of ichthyosis. Cardiac rhythm abnormalities have been previously reported in X-linked ichthyosis,[4,43] however in our study was noted in CBIE (12.6%) and unspecified ichthyosis (12.6%). Cardiac rhythm abnormalities were also noted in IV (14.3%). These associated comorbidities suggest that further clinical screening questions may help identify otherwise overlooked medical conditions in patients with ichthyoses.

48.1% of our cohort are within the two lowest deprivation quintiles. This finding likely reflects significant health inequalities,[44] barriers to specialist care[45] and the known shortfall of dermatologists in England with wide geographic variation in access to services.[46] Patient narratives suggest that living with ichthyosis or being a carer for someone with an ichthyosis could affect lifetime earnings potential.[47] This is especially important in systems outside the NHS where costs of prescriptions may be borne by patients and families.[48]

Patients who described themselves as having Asian ancestry and in particular Pakistani, but not Indian ancestry for example, were also significantly overrepresented in our cohort; this was enriched in autosomal recessive ichthyoses such as LI. Possible explanations for this include cultural practices such as marriage between parentally related individuals.[49] Notably a recent report in 2026 highlighted higher proportions of child deaths in children born with Pakistani ancestry but not in other ancestries in England.[50] These findings highlight the need for sensitive, culturally appropriate counselling and education and also should be considered when designing services and advocating for patients.

We demonstrate that patients living with ichthyosis are overall younger and more likely to die at a younger age than the reference population. A frequent recorded cause was cerebral palsy (CP). We also found high proportions of CP diagnoses amongst the cohort, particularly in the 'other' and 'unspecified' (which contain the syndromic ichthyoses) and XLI subtypes. There are several syndromic ichthyoses with CP or similar neurological features, particular those caused by ceramide synthesis disorders such as *ALDH3A2*-sEDD (Sjogren Larsson)[3] or *ELOVL1*-sEDD[51]. Reduced placental STS in XLI can cause prolonged labour[43] and there is an overall association between the ichthyoses and premature delivery[52]; difficult and premature labours are risk factors for cerebral palsy.[53] Congenital ichthyosis was the third most frequently recorded underlying cause of death in under 25 year olds, highlighting the potentially devastating impact of these conditions.

The estimated genetic testing rate of 80 tests per year nationally is relevant given the proposed changes to nomenclature towards dyadic diagnostic labels.[1–3] The percentage of patients with a positive result (56%) met clinical diagnostic criteria for inherited ichthyoses,

and this may give an indication of the yield of genetic testing which will be needed to inform reclassified diagnosis. Deprivation levels of the cohort having genetic testing were similar to the overall cohort (Table S8) and may be different in other healthcare systems where patients need to pay for genetic testing. Our data revealed age disparities in access to genetic testing, with only 13% of tests occurring in adults 40 years and older, compared to 37.5% in under 5. Emerging EDD clinical trials require patients to be genotyped, and older patients are therefore at risk of being excluded from trial opportunities.

Our work has limitations: A large proportion of our cohort are labelled as having an 'unspecified congenital ichthyosis'. This is a limitation of our dataset not containing ORPHAnet codes as part of routinely collected healthcare data.

The validated cases represented a limited sample of the entire cohort (337 of 4330 (7.8%)), which is in keeping with other similar NDRS studies in rare autoimmune and rheumatological disease (0.44% cases validated)[19,20]; non-validated cases are similarly retained in the epidemiological analyses of our study. The variability in the ichthyosis subtype specific validation is reflected in positive predictive values (PPVs) ranging from 24.1% for CBIE to 64.7% for LI. Of note another smaller Danish national ichthyosis study found an overall PPV of 74.7%; 95% CI: 69.0–79.7 and a subtype specific PPV ranging from 0 to 96.6%.[15] These PPV figures are a minimum figure, and must be considered when drawing subtype specific conclusions. Despite this there are subtype specific findings in our data which correspond with known associations and support its robustness: the highest proportions of neurodevelopmental disorders[54] and atopic disorders[13] are in the XLI and IV groups respectively. Further supportive evidence is provided by an English study utilising HES data alongside primary care data, which found similar prevalence rates of LI, CBIE and HI. These findings suggest these subtype specific proportions are reproducible across different studies and datasets.[55]

Our approach to co-morbidity prevalence estimation required we used routinely collected NHS secondary care data; these findings may therefore be affected by diagnostic coding, referral patterns and surveillance bias. This approach also means that certain conditions that are managed by family physicians may be underestimated, such as some mental health disorders. It is important to note that our cohort's median age of 22 years is substantially lower than the general English population median of 41 years. Consequently, the significantly higher prevalence rates for typically age-associated conditions such as atrial fibrillation and rheumatoid arthritis may be an underestimate. However, given the limited validation group, subtype specific comorbidity rates should be interpreted conservatively.

Regarding mortality, cerebral palsy and congenital ichthyosis are chronic underlying conditions rather than immediate causes of death; however, death certificate data are subject to limitations and frequently include existing major diagnosis when reporting cause of death. [56] Cerebral palsy and congenital ichthyosis may represent underlying or contributing diagnoses rather than proximate causes of death. These data may be a signal of severe disease burden rather than direct causal attribution.

We reported *STS*, *TGM1* and *NIPAL4* as the three most frequent positive test results of rare ichthyoses during the study window (Table 3 – GOSH data). Differing frequencies of affected genes have been reported by others[18,57] and may be explained by genetic test methodologies, ascertainment bias and population characteristics of these studies. Other genotyped cohort studies have addressed comorbidities in part; The largest study of 1000 kindreds identified *TGM1*, *KRT10, ABCA12* as the most commonly affected genes however ocular and hearing problems were the only non-dermatological published comorbidities.[18] A Polish study of 265 patients identified causal variants in 85% of cases with pathogenic variants in *ALOX12B, TGM1* and *FLG* being most frequent, however extra cutaneous comorbidities were not reported.[57] Hotz *et al*.[58] studied 64 patients with *ABCA12* PVs and found truncating PVs were more likely to be linked to the HI phenotype and missense linked to the LI/CIE phenotype but did not describe systemic comorbidities. In a further multicentre retrospective survey[38], a 44% infant mortality rate was found in 45 carriers of PVs of *ABCA12* with 3/45 reporting an inflammatory arthritis as a comorbidity. As more patients are genotyped in England future studies will be able to combine broad ascertainment and comorbidity analysis with detailed genotyping.

This national study provides the most comprehensive epidemiological analysis of ichthyoses in England to date, identifying substantial recorded disease burden, high rates of extracutaneous co-morbidities, and premature mortality. Genetic testing rates, relevant given the recent dyadic classification highlight the need for improved access to genetic testing. These data have important implications for service planning, research prioritisation, and addressing health inequalities in this historically neglected group.

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Figure legends

Figure 1 (a) CONSORT flow chart detailing cohort creation and (b) diagram detailing demographic extraction

Figure 2 Prevalence of the inherited ichthyoses across English regions.

Supplementary files

Figure S1 Disparity in self-described ethnicity in autosomal recessive lamellar ichthyosis.

Figure S2 Most frequently prescribed categories of prescriptions

Figure S3 A comparison of prevalences with other studies.

Table S1 ICD-10 codes used to identify ichthyoses and comorbidities. (a) Available ichthyosis codes in the ICD 10 classification system and indicative epidermal differentiation disorders (EDDs). (b) ICD-10 codes used to identify comorbidities.
Table S2 Genes evaluated on the NHS National Genomic Test Directory panel for inherited ichthyosis and erythrokeratoderma (R165)
Table S3 Ichthyosis ORPHAnet and ICD-10 code mapping terms for validation.
Table S4 Results of case validation. Number of cases validated across 5 hospitals in England. These results detail how many of the validated cases had any type of ichthyosis.
Table S5 Comparison between observed ethnicity proportions (overall cohort) and expected (England's population).
Table S6 Twenty most frequently recorded cause of death across all ichthyosis patients. Reference population data are the national percentages for England 2012-2023.
Table S7 Six most frequently recorded cause of death in under 25 year olds.
Table S8 Demographics of patients with reported genetic tests.
Supplementary Method

Table 1 Demographics of the overall cohort and ichthyosis subtypes.

	Overall n(%)	X-linked n(%)	Lamellar n(%)	CBIE n(%)	Harlequin n (%)	Other n(%)	Unspecified n(%)	IV n(%)
Sex								
Male	2517(58.1%)	269(82.8%)	179(56.6%)	174(32.2%)	101(39.5%)	188(54.5%)	1251(63.3%)	355(62.1%)
Female	1813(41.9%)	56(17.2%)	137(43.4%)	367(67.8%)	155(60.5%)	157(45.5%)	724(36.7%)	217(37.9%)
Vital Status (at 1st June 2023)								
Alive	3429 (79.2%)	303 (93.2%)	291 (92.1%)	353 (65.2%)	231 (90.2%)	295 (85.5%)	1503 (76.1%)	453 (79.2%)
Dead	901 (20.8%)	22 (6.8%)	25 (7.9%)	188 (34.8%)	25 (9.8%)	50 (14.5%)	472 (23.9%)	119 (20.8%)
Diagnoses								
n(%)	4330	325 (7.5%)	316 (7.3%)	541 (12.5%)	256 (5.9%)	345 (8.0%)	1975 (45.6%)	572 (13.2%)
Prevalence/million [95% CI]	59.4 [57.5-61.5]	5.3 [4.7-5.9]	5 [4.5-5.7]	6.1 [5.5-6.8]	4 [3.5-4.6]	5.1 [4.5-5.7]	26.1 [24.8-27.4]	7.9 [7.1-8.6]
Self-described ethnicity								
White	3070 (70.9%)	247 (76.0%)	140 (44.3%)	435 (80.4%)	200 (78.1%)	216 (62.6%)	1441 (73.0%)	391 (68.4%)
Asian	741 (17.1%)	29 (8.9%)	128 (40.5%)	67 (12.4%)	32 (12.5%)	86 (24.9%)	304 (15.4%)	95 (16.6%)
Black	191 (4.4%)	8 (2.5%)	20 (6.3%)	12 (2.2%)	6 (2.3%)	15 (4.3%)	91 (4.6%)	39 (6.8%)
Other	118 (2.7%)	8 (2.5%)	17 (5.4%)	8 (1.5%)	4 (1.6%)	13 (3.8%)	51 (2.6%)	17 (3%)
Mixed	110 (2.5%)	21 (6.5%)	9 (2.8%)	7 (1.3%)	6 (2.3%)	12 (3.5%)	37 (1.9%)	18 (3.1%)
Not Known	100 (2.3%)	12 (3.7%)	2 (0.6%)	12 (2.2%)	8 (3.1%)	3 (0.9%)	51 (2.6%)	12 (2.1%)
Deprivation quintile (IMD)								
1 (most deprived)	1165 (26.9%)	71 (21.8%)	120 (38.0%)	120 (22.2%)	70 (27.3%)	101 (29.3%)	544 (27.5%)	139 (24.3%)
2	918 (21.2%)	57 (17.5%)	76 (24.1%)	108 (20.0%)	57 (22.3%)	82 (23.8%)	403 (20.4%)	135 (23.6%)
3	839 (19.4%)	79 (24.3%)	59 (18.7%)	103 (19.0%)	39 (15.2%)	64 (18.6%)	365 (18.5%)	130 (22.7%)
4	739 (17.1%)	55 (16.9%)	37 (11.7%)	111 (20.5%)	46 (18.0%)	55 (15.9%)	346 (17.5%)	89 (15.6%)
5 (least deprived)	656 (15.2%)	59 (18.2%)	21 (6.6%)	99 (18.3%)	44 (17.2%)	43 (12.5%)	311 (15.7%)	79 (13.8%)
Not Known	13 (0.3%)	4 (1.2%)	3 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (0.3%)	0 (0.0%)
	Overall	**X-linked**	**Lamellar**	**CBIE**	**Harlequin**	**Other**	**Unspecified**	**IV**
Median age (IQR)	22 (38)	16 (21.5)	13 (13.5)	35 (49)	15 (41)	17 (22)	26 (44)	26 (39)
Median age at death (IQR)	74 (35)	80 (10)	0 (62)	76.5 (17.5)	0 (32)	19.5 (33)	77 (31)	72 (24)

Table 2 Proportion of cohort with a comorbidity of interest. Comorbidity prevalence for the overall cohort and each ichthyosis subtype were derived from HES ICD-10 coding on inpatient and outpatient episodes.

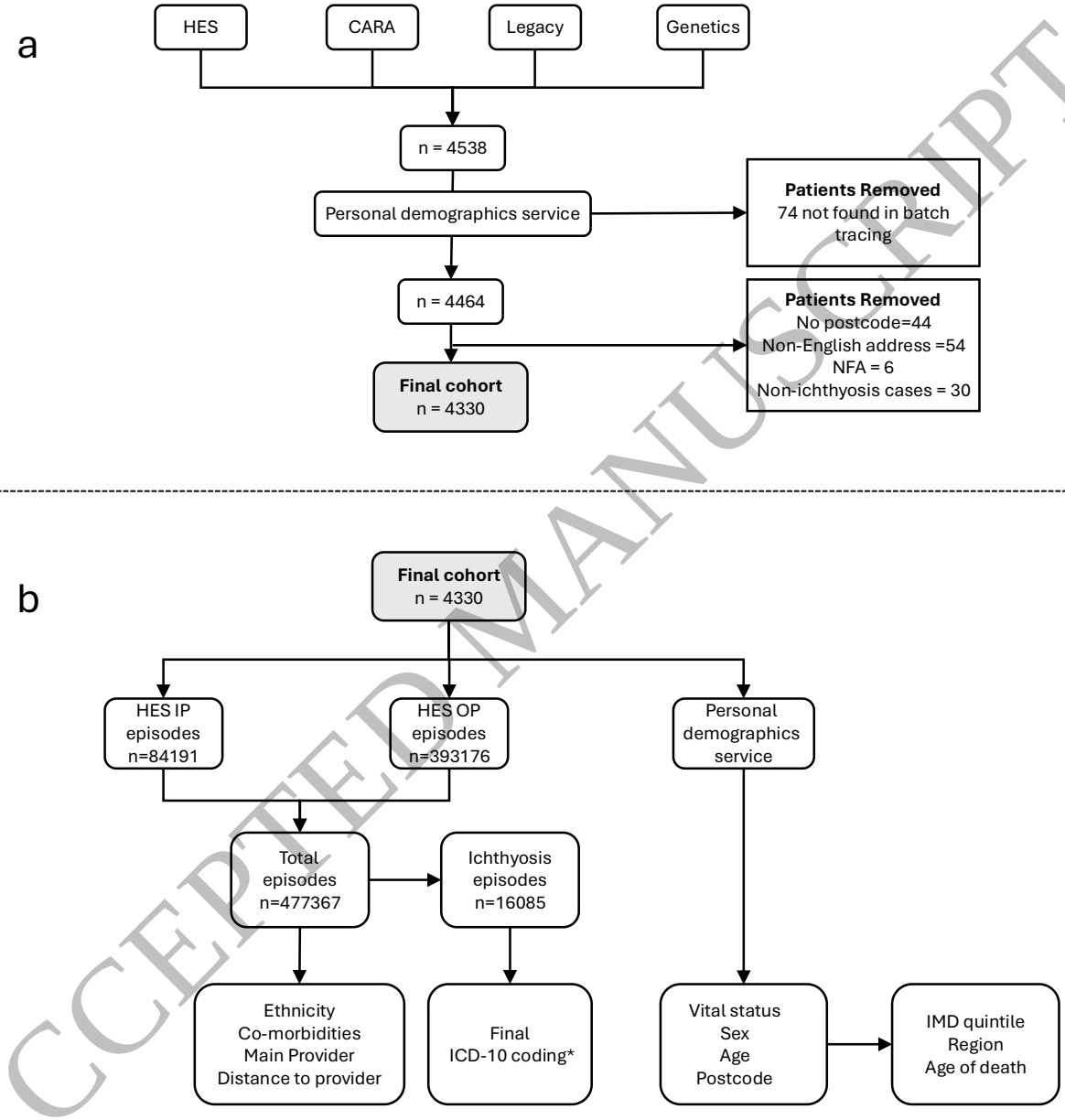
Comorbidity	Rare N=3758 n(%)	XLI n(%)	LI n(%)	CBIE n(%)	HI n(%)	Other n(%)	Unspecified congenital n(%)	IV N=572 n(%)	Overall N=4330 (%)
Asthma	706 (18.8%)	61 (18.8%)	22 (7.0%)	115 (21.3%)	37 (14.5%)	60 (17.4%)	411 (20.8%)	173 (30.2%)	879 (20.3%)
Skin infection (bacterial)	603 (16.0%)	28 (8.6%)	48 (15.2%)	126 (23.3%)	23 (9.0%)	58 (16.8%)	320 (16.2%)	104 (18.2%)	707 (16.3%)
Depression group	404 (10.8%)	27 (8.3%)	13 (4.1%)	86 (15.9%)	30 (11.7%)	24 (7.0%)	224 (11.3%)	65 (11.4%)	469 (10.8%)
IP	387 (10.3%)	10 (3.1%)	8 (2.5%)	151 (27.9%)	16 (6.3%)	9 (2.6%)	193 (9.8%)	66 (11.5%)	453 (10.5%)
-----RA	159 (4.2%)	<5	<5	96 (17.7%)	5 (2.0%)	<5	50 (2.5%)	17 (3.0%)	176 (4.1%)
AF	362 (9.6%)	20 (6.2%)	<5	68 (12.6%)	12 (4.7%)	9 (2.6%)	249 (12.6%)	82 (14.3%)	444 (10.3%)
Type 2 diabetes	332 (8.8%)	15 (4.6%)	<5	66 (12.2%)	10 (3.9%)	10 (2.9%)	227 (11.5%)	64 (11.2%)	396 (9.2%)
Rhinitis	101 (2.7%)	10 (3.1%)	<5	15 (2.8%)	<5	15 (4.3%)	55 (2.8%)	50 (8.7%)	151 (3.5%)
Autism/ Asperger's	96 (2.6%)	17 (5.2%)	9 (2.8%)	7 (1.3%)	<5	11 (3.2%)	49 (2.5%)	21 (3.7%)	117 (2.7%)
Herpes infections	61 (1.6%)	<5	<5	10 (1.8%)	<5	12 (3.5%)	30 (1.5%)	29 (5.1%)	90 (2.1%)
Food allergies	54 (1.4%)	<5	<5	11 (2.0%)	<5	21 (6.1%)	17 (0.9%)	22 (3.8%)	76 (1.8%)
Type 1 diabetes	60 (1.6%)	5 (1.5%)	<5	14 (2.6%)	<5	<5	37 (1.9%)	12 (2.1%)	72 (1.7%)
ADHD	48 (1.3%)	18 (5.5%)	7 (2.2%)	<5	<5	<5	18 (0.9%)	11 (1.9%)	59 (1.4%)
Cerebral palsy	344 (9.2%)	18 (5.5%)	8 (2.5%)	17 (3.1%)	8 (3.1%)	91 (26.4%)	202 (10.2%)	20 (3.5%)	364 (8.4%)

To maintain patient confidentiality, counts less than 5 are suppressed. XLI (X-linked ichthyosis),LI (lamellar ichthyosis), CBIE (congenital bullous ichthyosiform erythroderma), HI (harlequin ichthyosis), IV (ichthyosis vulgaris), IP (inflammatory polyarthropathies) see Table S1b for list, RA (rheumatoid arthritis), AF (atrial fibrillation and flutter), ADHD (attention-deficit hyperactivity disorders).

Table 3 National genetic testing results for ichthyosis patients 2021-2024.
The total number of ichthyosis genetic tests performed nationally, and results of 160 cases tested at one of the two national Genomic Laboratory Hubs (Great Ormond Street Hospital-GOSH). Variant data is provided for reportable findings at aggregate level within the requirements of anonymity preservation (k>5). VUS, variant of uncertain significance.

Patient level contract monitoring (PLCM) data:	**n(%)**
Total tests in England 2021-2024	312
Performed at Great Ormond Street Hospital (GOSH)	168 (53.8%)
Available GOSH data (January 2021 – September 2024):	160 (95.2%)
Pathogenic/positive (%)	90 (56.3%)
VUS (%)	16 (10.0%)
No pathogenic variant (%)	54 (33.7%)
Pathogenic variants found in the positive cases (n=90):	No. (%)
STS	16 (17.8%)
FLG	12 (13.3%)
TGM1	11 (12.2%)
NIPAL4	9 (10.0%)
ALOXE3	5 (5.6%)
Genes affecting fewer than 5 patients are grouped to maintain confidentiality: *ABCA12, CARD14, CERS3, DSP, GJB3, GJB2, GJB4, KRT1, KRT6A, KRT6B, KRT6C, KRT10, KRT17, LOR, PNPLA1, SLC27A4, SPINK5, SULT2B1, WNT10A*	37(41.1%)

Figure 1 (a) CONSORT flow chart detailing cohort creation and (b) diagram detailing demographic extraction



Key: HES (Hospital episode statistics), ICD-10 (International Classification of Diseases 10), CARA (NDRS congenital anomaly registry), legacy (regional legacy congenital anomaly registration data), NFA (no fixed abode), IP (inpatient episodes), OP (outpatient episodes), IMD (indices of multiple deprivation). *Legacy n=82 and CARA n=140 diagnoses are favoured over HES diagnoses as they have been verified by clinicians at time of registration. When multiple competing diagnoses or demographics were available, the most frequent was favoured, and then the most recently recorded in case of ties.

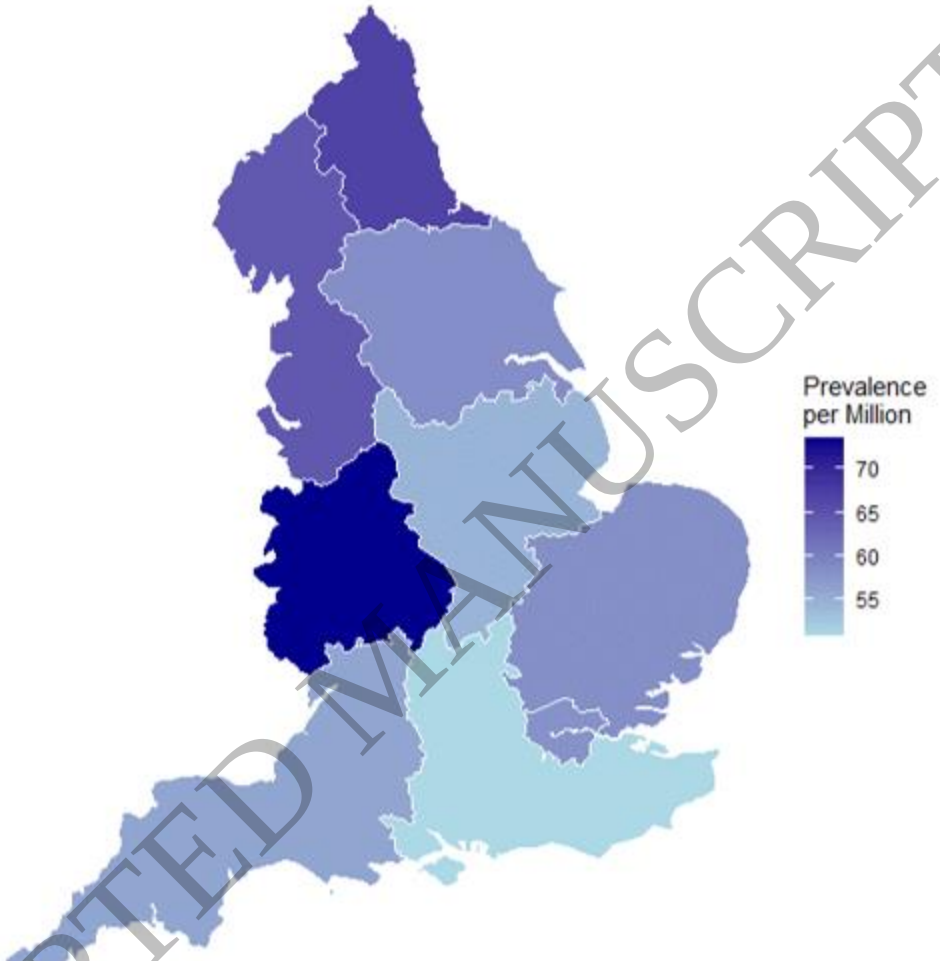


Figure 1
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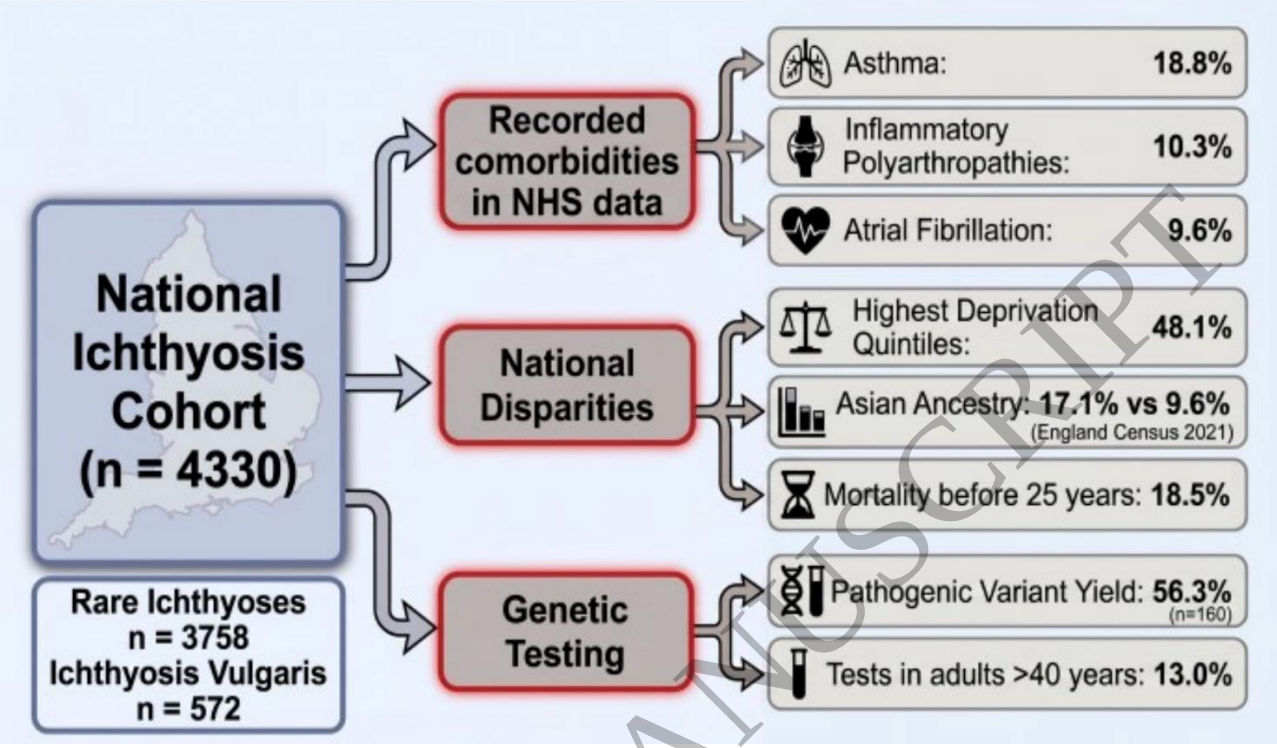

Graphical Abstract