IMPERIAL COLLEGE HEALTH PARTNERS

A preliminary assessment of the potential impact of rare diseases on the NHS

Mendelian

Report on Initial Findings
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Project Background

Rare diseases (RD) are an increasingly recognised health priority due to their impact, severity and burden on the patient, their family and the health system [1].

Most RD are genetically inherited and they can be particularly difficult to diagnose due to their individual rareness. Orphanet – a European portal for rare diseases and orphan drugs – considers a RD to have a prevalence no more than 1 in 2,000 in the European population [2]. This can include rare auto-immune conditions and cancers. Other causes of RD include infections, allergies and teratogenic effects [1].

The 2015 Policy Innovation Research Unit (PIRU) report into RDs highlights that achieving a differential diagnosis for a RD often relies on the availability of an accessible/reliable laboratory or genetic test and/or access to an appropriately experienced clinician [3]. This means that the prolonged journey to medical diagnosis experienced by many patients with a RD can involve serial referrals to several specialists alongside a plethora of, often invasive, tests. This diagnostic delay can reach up to 30 years for some conditions [3].

Orphanet estimates that six- to seven-thousand rare diseases have been discovered and new diseases are regularly described in the medical literature. However, they also point out that the number of individually diagnosed diseases depends on the degree of specificity used when classifying the different entities/disorders [2].

Many RD can be detected in childhood, but it is thought that around 50% don't fully manifest symptomatically until adulthood [4]. People with rare diseases tend to have multiple health problems and complex care needs requiring access to a wide range of health services [1].

Despite the global prioritisation of RD, very few comprehensive impact analyses have been conducted at the population-level to evaluate the healthcare burden of RD, and more specifically the time period prior to diagnosis; and their contribution to overall healthcare resource utilisation and healthcare costs [5].

The ability to undertake such an analysis is confounded by the fact that routine healthcare data collection does not accurately capture and identify the thousands of different RD classifications that can pass through a healthcare system. For example, the International Classification of Diseases (ICD-10) is believed to only account for approximately 5% of known RD [2,6].

Orphanet offers a more comprehensive coding system for RD (Orpha codes). The Orpha codes have been used to inform the updated ICD-11 coding, released in June 2018, but this has not yet been widely implemented across routine data collection systems [6].

Project Scope and Objectives

This project was established to perform a preliminary investigation into the potential cost and resource impact of RD on the NHS, with a focus on the time period up to diagnosis, using reported real-world hospital datasets (HES data) in England.

Methods

The challenge of appropriate coding for RD within the HES database was confirmed early in the project. HES coding is based on the ICD-10, which, as discussed, is believed to only account for approximately 5% of RDs [3]. Furthermore, multiple diseases, including RDs, can often share the same ICD-10 coding.

For the purposes of this analysis, the methodology first reported by Walker et al [4], was adopted to use discrete ICD-10 codes that are known to account for only one RD per code, and not overlap with any other medical condition. This resulted in the analysis of a total of 426 RD codes crossing a range of bodily systems and clinical specialties. See Appendix I for the list of all HES ICD-10 codes used in this analysis.

This approach ensured that only accurately diagnosed and reported RD were included in the dataset. However, it also means that only a small proportion of the 5,400 RDs currently listed in the Orphanet database [6] will be accounted for in this preliminary analysis.

Aggregated statistical reports from the HES database were used to identify patients of all ages receiving their first diagnosis with one of these 426 specific RD diagnostic codes over a 12-month period from April – March 2017/18 (the HES data reporting cycle). Data were aggregated at the patient record level using HES identification numbers, which enabled a longitudinal analysis across the hospital system and ensured no ‘double counting’ in the analysis.

The hospital activity levels and costs were then collated for this patient cohort for the preceding 10 years. Note this is a maximum of 10 years, but will be a range of 9 to 10 years, depending on the time of diagnosis during 2017/18. The HES database contains compiled details of all admissions, outpatient appointments, hospital day cases, and A&E attendances at NHS hospitals in England [7]. Each of these activities were included in our hospital activity analysis and used to calculate hospital resource utilisation and costs allocated to this RD patient cohort over the preceding 10-year period.

Comparators

The data comparator for this preliminary analysis was selected as the total remaining hospital population identified through the HES database with a hospital episode (admission or attendance) during the 2017/2018 period. The only inclusion criterion for the comparator group was any hospital episode (admission or attendance) during the 2017/18 HES data reporting period. The single exclusion criterion was that the patient had not been allocated one of the 426 RD ICD-10 diagnostic codes at any time. The non-specific nature of ICD-10 coding for RD means that the comparator cohort will include patients with other RDs (diagnosed and undiagnosed), as well as other complicated/costly conditions such as cancer or trauma patients.

It should also be noted that not every hospital episode recorded in 2017/2018 in this comparative cohort will be related to a diagnostic code, and, as a consequence, the patients included in this comparative cohort will be at a variety of different stages in their particular care pathway.

Ten-year hospital activity level and cost data for this population cohort were also calculated, although population-matched comparisons between these two groups remains limited due to the reasons stated above and below. Further epidemiological research is required to identify the best matched comparator(s), before further comparative conclusions can be drawn.

The analysis has only been designed to enable a preliminary cost impact assessment. Importantly, the comparative cohort will only represent a proportion of the total hospital population during the 10-year period, as it only contains patients who had a hospital activity during 2017/18. It does not therefore enable a cost comparison of population-based ratios or percentages to be evaluated against the full HES database hospital population during this 10-year period. This could ideally be investigated further in a future analysis.

Additional analyses

1. Age-related sub-analysis

In addition, subgroups of the RD and comparator patient cohorts were analysed based on age ≤ 10 years of age at diagnosis. These two age-matched cohorts will include a longitudinal analysis of any HES-reported episodes during the entire life of a patient and are likely to be more homogeneous and closely matched at a population level. It also avoids the data being disproportionately spread across a wide age range, with multiple complicating factors that might not be closely matched.

2. Diagnostic procedures

A top 50 procedures analysis (in-patient, out-patient and A&E) was also performed for all ages, based on the number of episodes in the RD population. Those coded as a diagnostic procedure (and therefore considered investigative in nature) were specifically identified and compared with the remaining 2017/2018 HES database patient population.

Cost data caveats

1. The term *'HES-reported inpatient / outpatient hospital population'* referred to in this report relates to all individual admissions, outpatient appointments, hospital day cases, and A&E attendances at NHS hospitals in England reported in the HES database, and aggregated at patient record level. This covers both secondary and tertiary hospital-based specialist care. The cost data and *'attendance / spells'* counts were based on these activities.

2. The cost datasets included in the calculations are based on the 'payment by results' tariff and are therefore likely to underestimate any high-cost conditions.

3. Patient medical care in the primary care (GP) setting was not within the scope of this analysis, and the datasets do not include any primary care costs, which are expected to be an important component of the RD diagnostic process. In the future, a linked dataset analysis between primary care and hospital costs would provide a more comprehensive evaluation of the impact of RDs versus other conditions, and provide a more accurate estimate of the overall pre-diagnostic health system burden of these patients.

4. The cost calculations included in this analysis do not include either in-patient or out-patient drug treatment costs (excluded from tariff or those prescribed in primary care), which are known to be high for the RD population [8]. These costs were considered to be outside the scope of this evaluation, which focuses on hospital activity prior to diagnosis.

Research Findings

The following tables and figures provide an overview of the key findings from this preliminary investigation into the potential cost and resource impact of diagnosing RD on the NHS.

Table 1: Patient Numbers

Patient type	2017/18 cohort patient count (all ages)	2017/18 cohort patient count (age ≤ 10 years at diagnosis)	Previous 10-year patient count (all ages)*
RD diagnosis patient cohort	258,235	38,155	2,197,501
Remaining HES-reported population (comparator)	27,212,885	3,535,280	66,444,153
Total HES-reported inpatient or outpatient population	27,471,120	3,573,435	68,641,654
RD cohort as a percentage of the overall HES-reported inpatient or outpatient population	0.94%	1.07%	3.20%

*All patients in the HES database during this period

In the last 10 years, a total of 2,197,501 unique patient IDs were linked to one of the 426 RD ICD-10 codes, comprising 3.2% of the overall HES-reported inpatient / outpatient hospital population.

In terms of new diagnoses during the HES-reporting period 2017/18, this totalled 258,235 patients, or 0.94% of the overall inpatient or outpatient hospital population during this period.

We would expect that the 10-year patient data would provide a more accurate epidemiological picture of the overall prevalence of the 426 RD included in this evaluation.

Of the RD diagnosis patient cohort 15% were ≤ 10 years of age; 1.07% of the overall age-matched 2017/18 population.

NOTE: An additional analysis to evaluate which of the 426 RD codes were present in this younger patient population was not conducted at this stage. However, this should be reviewed in any future assessments.

Table 2: Cost impact over previous 10 years

Patient type*	Total cost**	Average cost per patient	Total spells / hospital attendances
RD diagnosis patient cohort	£3,373,549,556	£13,064	1,763,232
Comparator population***	£160,824,675,288	£5,910	88,518,143

*2017/18 HES-reported inpatient or outpatient population

**See cost data caveats

***This is a mixed population that could have been diagnosed at any time and does not enable direct comparison of pre-diagnostic costs.

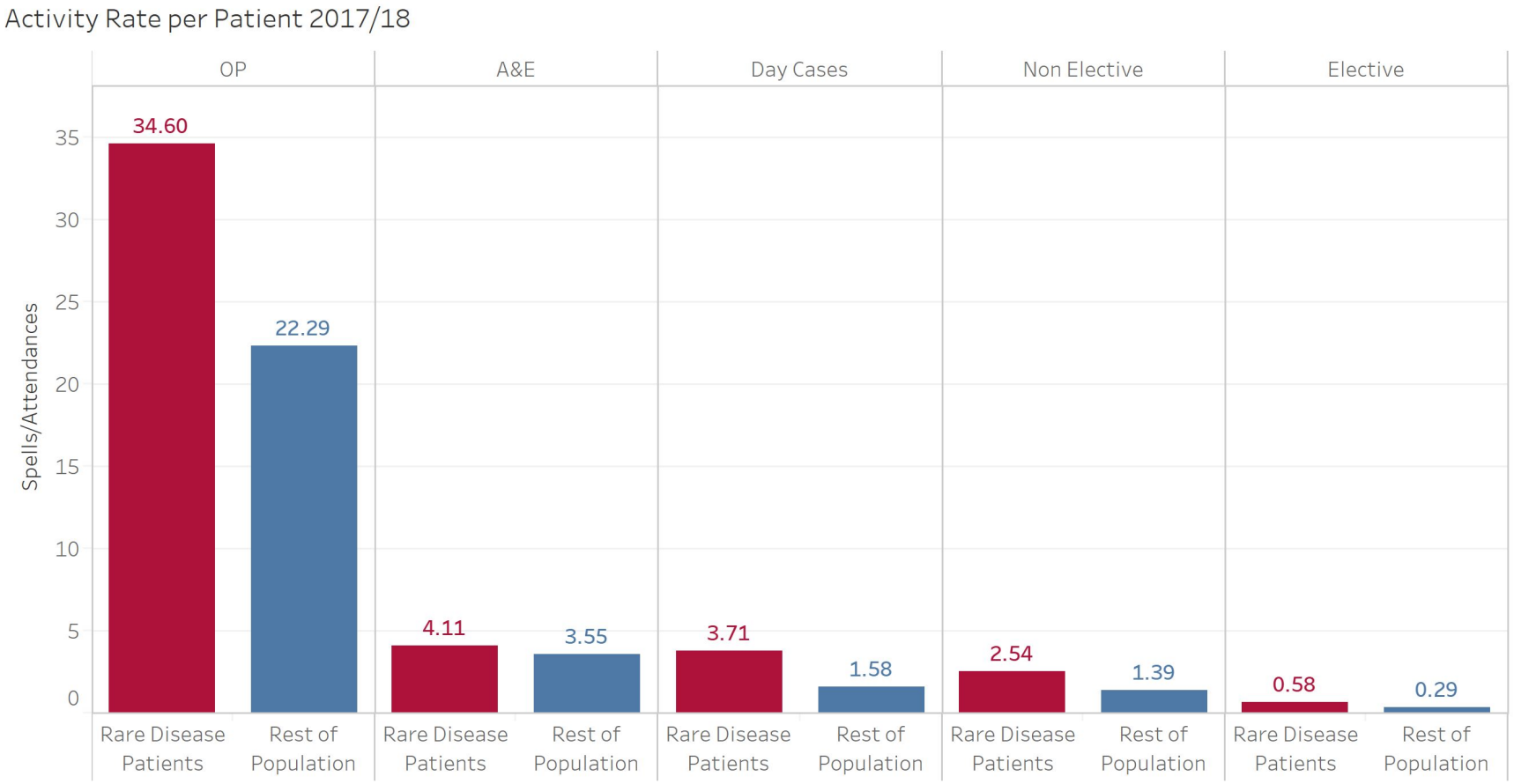
The breakdown of spells / attendance during the preceding 10 years by resource – non-elective, elective, day case, outpatient appointment and A&E attendance is provided in Table 3 and Figure 1.

Table 3: Resource utilisation over previous 10 years – all ages

Patient type*	Patient count	Total spells or attendances	Outpatient appointments	A&E attendances	Total spells – day case	Total spells – non-elective	Total spells – elective
RD diagnosis patient cohort	258,235	1,763,232	8,935,952	1,061,528	958,380	655,084	149,768
Average per patient		6.83	34.60	4.11	3.71	2.54	0.58
Comparator population	27,212,885	88,518,143	606,497,030	96,579,217	42,905,063	37,799,624	7,813,456
Average per patient		3.25	22.29	3.55	1.58	1.39	0.29

*2017/18 HES-reported inpatient or outpatient population

Figure 1: Average activity rate per patient over previous 10 years – all ages



OP: out-patient; A&E: Accident and Emergency; Non-elective: emergency / unplanned procedures; Elective: planned / scheduled procedures

Table 4: Evaluating specific sub-populations – ≤10 years of age at diagnosis

Patient type*	Patient count	Total cost over 10 years	Average cost per patient over 10 years	Total spells / attendance over 10 years
RD diagnosis patient cohort	38,155	£355,879,086	£9,327	141,728
Comparator population	3,535,280	£7,918,190,781	£2,240	6,471,989

*2017/18 HES-reported inpatient or outpatient population

Table 5: Resource utilisation over previous 10 years – ≤10 years of age at diagnosis

Patient type*	Patient count	Total spells	Outpatient appointments	A&E attendances	Total spells – day case	Total spells – non-elective	Total spells – elective
RD diagnosis patient cohort	38,155	141,728	511,330	85,963	37,917	92,257	11,554
Average per patient		3.71	13.40	2.25	0.99	2.42	0.30
Comparator population	3,535,280	6,471,989	24,277,414	10,974,937	822,042	5,483,220	166,727
Average per patient		1.83	6.87	3.10	0.23	1.55	0.05

*2017/18 HES-reported inpatient or outpatient population

Table 6: In-patient diagnostic procedures (previous 10 years) – all ages

		RD diagnosis patient cohort*		Comparator population*	
OPCS Code	**OPCS Description****	**Total**	**Average per patient tariff cost*****	**Total**	**Average per patient tariff cost*****
U201	Transthoracic echocardiography	47,200	£10,486.89	826,425	£4,853.20
U202	Transoesophageal echocardiography	7,642	£8,886.20	136,875	£7,315.35
U071	Computed tomography of chest	6,406	£6,724.80	113,872	£4,210.46
Y973	Radiology with post contrast	47,126	£6,389.18	1,415,513	£4,150.65
Y981	Radiology of one body area (or < 20 minutes)	89,661	£6,335.40	3,273,664	£3,669.80
U051	Computed tomography of head	34,023	£6,065.87	1,402,316	£3,612.00
A559	Unspecified diagnostic spinal puncture	10,270	£6,038.47	335,898	£1,934.16
U212	Computed tomography NEC	42,388	£5,880.15	1,589,083	£3,763.85
Y752	Laparoscopic approach to abdominal cavity NEC	15,372	£5,784.56	1,270,596	£4,009.62
Y982	Radiology of two body areas	25,532	£5,682.32	1,024,307	£3,717.28
U052	Magnetic resonance imaging of head	14,131	£5,433.96	391,375	£3,537.77
U211	Magnetic resonance imaging NEC	9,944	£5,344.83	254,778	£3,666.80
Y983	Radiology of three body areas (or 20-40 minutes)	11,117	£5,331.03	269,679	£4,172.87
U354	Computed tomography of pulmonary arteries	9,273	£3,814.95	305,987	£2,735.09
W365	Diagnostic extraction of bone marrow NEC	16,512	£3,534.39	117,930	£1,191.17
X369	Unspecified blood withdrawal	16,874	£2,553.91	166,362	£1,491.67

		RD diagnosis patient cohort*		Comparator population*	
OPCS Code	**OPCS Description****	**Total**	**Average per patient tariff cost*****	**Total**	**Average per patient tariff cost*****
K634	Coronary arteriography using two catheters	10,847	£2,530.94	484,706	£1,834.23
K633	Angiocardiography of left side of heart NEC	4,959	£2,400.85	279,195	£1,804.29
G459	Unspecified diagnostic fibreoptic endoscopic examination of upper gastrointestinal tract	21,738	£1,807.97	1,127,645	£871.36
H251	Diagnostic endoscopic examination of lower bowel and biopsy of lesion of lower bowel using fibreoptic sigmoidoscope	8,162	£1,456.33	448,441	£874.33
G451	Fibreoptic endoscopic examination of upper gastrointestinal tract and biopsy of lesion of upper gastrointestinal tract	47,709	£1,016.04	2,585,774	£642.18
H259	Unspecified diagnostic endoscopic examination of lower bowel using fibreoptic sigmoidoscope	13,656	£950.61	1,021,670	£527.52
H221	Diagnostic fibreoptic endoscopic examination of colon and biopsy of lesion of colon	18,213	£824.48	1,178,838	£596.66
H229	Unspecified diagnostic endoscopic examination of colon	17,623	£729.60	1,290,476	£530.69
H201	Fibreoptic endoscopic snare resection of lesion of colon	7,683	£716.66	508,516	£630.84

*2017/18 HES-reported inpatient or outpatient population

**Table sorted in descending order based on average cost in the RD population

***A spell in hospital generates an HRG (Healthcare Resource Group) code with a specific tariff price attached. Not all spells for patients undergoing the same procedure generate the same HRG code and therefore the tariff price for each patient undergoing the same procedure can vary. This is due to the fact that many different factors can influence the tariff costs charged by the hospital to the CCG e.g. some patients will require a longer or shorter length of stay in hospital; for example, patients that stay in hospital longer than the specified time associated with an HRG incur a daily 'excess bed day fee'. Another factor that often influences the tariff price is the patients' age and comorbidities, such as diabetes for example, which the trust must manage alongside their main reason for admission.

Table 7: Out-patient diagnostic procedures (previous 10 years) – all ages

		RD diagnosis patient cohort*		Comparator population*	
OPCS Code	**OPCS Description**	**Total**	**Average per patient tariff cost****	**Total**	**Average per patient tariff cost**
X369	Unspecified blood withdrawal	44,593	£391.57	1,453,666	£209.34
X368	Other specified blood withdrawal	18,876	£326.89	881,986	£222.19
X363	Venous sampling	24,599	£293.95	1,101,057	£183.26
E921	Carbon monoxide transfer factor test	11,516	£285.79	309,337	£257.45
U328	Other specified diagnostic blood tests	25,177	£260.14	1,341,181	£173.16
Q555	Transvaginal ultrasound examination of female genital tract	12,300	£257.72	1,562,102	£236.01
U329	Unspecified diagnostic blood tests	24,338	£233.86	1,368,279	£159.08
U262	Uroflowmetry NEC	8,621	£231.82	591,319	£221.44
U124	Ultrasound of bladder	7,361	£216.48	510,935	£201.62
U263	Test strip urinalysis	26,960	£205.86	2,433,608	£175.36
C873	Tomography evaluation of retina	73,128	£198.49	5,970,909	£191.53
E369	Unspecified diagnostic endoscopic examination of larynx	13,100	£191.09	919,797	£178.42
E253	Diagnostic endoscopic examination of nasopharynx NEC	13,742	£188.54	1,016,181	£178.05
H289	Unspecified diagnostic endoscopic examination of sigmoid colon using rigid sigmoidoscope	6,987	£184.13	537,106	£184.22
U199	Unspecified diagnostic electrocardiography	40,741	£183.49	1,876,801	£154.70
C871	Digital imaging of retina	13,578	£170.64	1,129,625	£162.88
U198	Other specified diagnostic electrocardiography	15,286	£165.21	855,633	£147.78
U201	Transthoracic echocardiography	59,781	£164.88	2,021,972	£123.22

		RD diagnosis patient cohort*		Comparator population*	
OPCS Code	**OPCS Description**	**Total**	**Average per patient tariff cost****	**Total**	**Average per patient tariff cost**
E932	Spirometry	23,170	£162.78	908,543	£111.08
S605	Diagnostic dermatoscopy of skin	10,574	£155.14	957,164	£146.31
U192	24-hour ambulatory electrocardiography	15,197	£150.05	844,232	£143.51
U209	Unspecified diagnostic Echocardiography	7,014	£131.83	301,917	£113.72
U216	Ultrasound scan NEC	37,229	£93.80	2,895,994	£96.93
U241	Pure tone audiometry	16,890	£92.51	1,356,678	£87.47
U243	Hearing assessment	9,197	£91.97	682,598	£84.26
U217	Plain X-ray NEC	28,449	£79.37	2,418,338	£66.77
Y981	Radiology of one body area (or < 20 minutes)	171,782	£79.34	11,561,110	£64.67
U073	Plain x-ray of chest	22,788	£77.88	1,186,259	£37.05
U134	Plain x-ray of joint	13,775	£74.12	1,327,871	£60.61
U082	Ultrasound of abdomen	11,101	£54.36	647,216	£45.90
U131	Bone densitometry	6,971	£50.51	481,402	£61.22
Y973	Radiology with post contrast	34,023	£43.68	1,336,730	£38.89
U212	Computed tomography NEC	32,556	£43.16	1,318,891	£40.67
Y983	Radiology of three body areas (or 20-40 minutes)	19,033	£40.68	829,233	£39.53
Y982	Radiology of two body areas	19,069	£38.41	1,168,658	£41.56
U071	Computed tomography of chest	6,396	£28.85	245,113	£26.33

		RD diagnosis patient cohort*		Comparator population*	
OPCS Code	**OPCS Description**	**Total**	**Average per patient tariff cost****	**Total**	**Average per patient tariff cost**
U052	Magnetic resonance imaging of head	9,993	£24.23	501,258	£17.08
U211	Magnetic resonance imaging NEC	23,148	£23.40	1,313,262	£19.43
U133	Magnetic resonance imaging of bone	6,106	£22.95	583,127	£19.54

*2017/18 HES-reported inpatient or outpatient population

**Table sorted in descending order based on average cost in the RD population

Discussion

This initial assessment of the impact of pre-diagnosis RD on the NHS was performed using a relatively small RD population accounted for by 426 ICD-10 diagnostic codes that provide a discrete RD diagnosis. As such, it provides an insight into the lengthy process of diagnosing rare diseases on the NHS in terms of resource utilisation and cost, and the potential overall impact on the patient.

The RD population included in this study was 258,235 patients out of a total reported inpatient or outpatient hospital population of 27,212,885 during the HES reporting year 2017/18 (approximately 1%).

This population totalled hospital costs of £3.4 billion, an average per patient cost of £13,000, during the 10 years prior to diagnosis. From the comparative data set (the remaining HES-reported inpatient or outpatient population during 2017/18) the average patient cost in the remaining population for this 10-year period was £5,910.

When the two sub-populations aged ≤10 years at the time of diagnosis were compared, the differences in the per patient costs became larger in magnitude for the RD population (£9,327 versus £2,240), as did differences in resource utilisation across the board. This provides a clear signal of the increased hospital costs associated with the pre-diagnosis RD population compared with this more closely age-matched comparative patient group.

Resource utilisation was particularly high in the outpatient setting for all RD patient groups – RD patients experienced an average of 35 outpatient procedures over 10 years, compared with 22 outpatient procedures in the comparative population.

Individuals with one of the RD diagnostic codes underwent a range of more costly investigative procedures during this period, both in the in-patient and outpatient setting. Particularly high rates of radiography procedures, such as cardiography and computed tomography, MRI, and invasive procedures such as laparoscopy and spinal puncture were seen in the RD cohort. The total cost for the RD cohort was higher than the costs of the comparative population for the majority of procedures.

This analysis represents a preliminary comparison of the RD population with other hospital patient populations. Ideally, more appropriate comparative patient cohorts (for example, less heterogeneous in terms of patient-type, demographics and time of diagnosis) can be identified for future comparisons.

In addition, this analysis highlighted the challenge of identifying a clearly-defined cohort of diagnosed RD patient within the hospital population (based on HES ICD-10 coding) that is representative of the overall RD patient population. It also emphasises the challenges and barriers to achieving a clear diagnosis experienced by RD patients and clinicians worldwide [3].

These data might well be extrapolated to consider the potential impact of the additional 5,000 RDs contained on the Orphanet database [5], in order to give a true picture of the impact of pre-diagnosis RD on the hospital system, both in terms of costs and resource utilisation. This impact is therefore likely to be considerably higher than the £3.4 billion identified for this small subset of patients. In addition to this is the cost of managing and treating these complex conditions once they are diagnosed.

Finally, when estimating the cost impact of diagnosing RDs on the NHS, consideration must also be given to the time spent undergoing investigation and treatment in the primary care system, prior to referral and/or emergency admission to secondary or tertiary care. To fully review the total cost impact of diagnosing RDs on the NHS a full analysis using linked datasets between primary, secondary and tertiary care would be desirable.

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Appendix I – ICD-10 codes

Code	Code Description
C15	Malignant neoplasm of oesophagus
C220	Malignant neoplasm: Liver cell carcinoma
C221	Malignant neoplasm: Intrahepatic bile duct carcinoma
C222	Malignant neoplasm: Hepatoblastoma
C46	Kaposi sarcoma
C570	Malignant neoplasm: Fallopian tube
C692	Malignant neoplasm: Retina
C740	Malignant neoplasm: Cortex of adrenal gland
C81	Hodgkin lymphoma
C82	Follicular lymphoma
C833	Diffuse large B-cell lymphoma
C84	Mature T/NK-cell lymphomas
C864	Blastic NK-cell lymphoma
C866	Primary cutaneous CD30-positive T-cell proliferations
C880	WaldenstrÃ¶m macroglobulinaemia
C882	Other heavy chain disease
C883	Immunoproliferative small intestinal disease
C884	Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue [MALT-lymphoma]
C910	Acute lymphoblastic leukaemia [ALL]
C920	Acute myeloblastic leukaemia [AML]
C921	Chronic myeloid leukaemia [CML], BCR/ABL-positive
C922	Atypical chronic myeloid leukaemia, BCR/ABL-negative
C924	Acute promyelocytic leukaemia [PML]
C931	Chronic myelomonocytic leukaemia
C933	Juvenile myelomonocytic leukaemia
C943	Mast cell leukaemia
C960	Multifocal and multisystemic (disseminated) Langerhans-cell histiocytosis [Letterer-Siwe disease]
D181	Lymphangioma, any site
D444	Neoplasm of uncertain or unknown behaviour: Craniopharyngeal duct
D448	Neoplasm of uncertain or unknown behaviour: Pluriglandular involvement
D45	Polycythaemia vera
D473	Essential (haemorrhagic) thrombocythaemia
D475	Chronic eosinophilic leukaemia [hypereosinophilic syndrome]
D55	Anaemia due to enzyme disorders
D560	Alpha thalassaemia
D561	Beta thalassaemia
D562	Delta-beta thalassaemia
D564	Hereditary persistence of fetal haemoglobin [HPFH]
D57	Sickle-cell disorders

Code	Code Description
D580	Hereditary spherocytosis
D581	Hereditary elliptocytosis
D588	Other specified hereditary haemolytic anaemias
D590	Drug-induced autoimmune haemolytic anaemia
D591	Other autoimmune haemolytic anaemias
D593	Haemolytic-uraemic syndrome
D595	Paroxysmal nocturnal haemoglobinuria [Marchiafava-Micheli]
D601	Transient acquired pure red cell aplasia
D640	Hereditary sideroblastic anaemia
D641	Secondary sideroblastic anaemia due to disease
D642	Secondary sideroblastic anaemia due to drugs and toxins
D643	Other sideroblastic anaemias
D644	Congenital dyserythropoietic anaemia
D66	Hereditary factor VIII deficiency
D67	Hereditary factor IX deficiency
D681	Hereditary factor XI deficiency
D71	Functional disorders of polymorphonuclear neutrophils
D751	Secondary polycythaemia
D80	Immunodeficiency with predominantly antibody defects
D81	Combined immunodeficiencies
D820	Wiskott-Aldrich syndrome
D821	Di George syndrome
D822	Immunodeficiency with short-limbed stature
D823	Immunodeficiency following hereditary defective response to Epstein-Barr virus
D83	Common variable immunodeficiency
D841	Defects in the complement system
D86	Sarcoidosis
E00	Congenital iodine-deficiency syndrome
E030	Congenital hypothyroidism with diffuse goitre
E031	Congenital hypothyroidism without goitre
E201	Pseudohypoparathyroidism
E220	Acromegaly and pituitary gigantism
E232	Diabetes insipidus
E24	Cushing syndrome
E25	Adrenogenital disorders
E26	Hyperaldosteronism
E301	Precocious puberty
E310	Autoimmune polyglandular failure
E340	Carcinoid syndrome
E345	Androgen resistance syndrome
E52	Niacin deficiency [pellagra]
E700	Classical phenylketonuria

Code	Code Description
E701	Other hyperphenylalaninaemias
E702	Disorders of tyrosine metabolism
E703	Albinism
E710	Maple-syrup-urine disease
E711	Other disorders of branched-chain amino-acid metabolism
E720	Disorders of amino-acid transport
E723	Disorders of lysine and hydroxylysine metabolism
E724	Disorders of ornithine metabolism
E730	Congenital lactase deficiency
E740	Glycogen storage disease
E741	Disorders of fructose metabolism
E742	Disorders of galactose metabolism
E750	GMâ,, gangliosidosis
E751	Other gangliosidosis
E752	Other sphingolipidosis
E753	Sphingolipidosis, unspecified
E754	Neuronal ceroid lipofuscinosis
E760	Mucopolysaccharidosis, type I
E761	Mucopolysaccharidosis, type II
E77	Disorders of glycoprotein metabolism
E782	Mixed hyperlipidaemia
E79	Disorders of purine and pyrimidine metabolism
E80	Disorders of porphyrin and bilirubin metabolism
E830	Disorders of copper metabolism
E831	Disorders of iron metabolism
E832	Disorders of zinc metabolism
E84	Cystic fibrosis
E85	Amyloidosis
F511	Nonorganic hypersomnia
F84	Pervasive developmental disorders
G10	Huntington's disease
G113	Cerebellar ataxia with defective DNA repair
G114	Hereditary spastic paraplegia
G120	Infantile spinal muscular atrophy, type I [Werdnig-Hoffman]
G122	Motor neuron disease
G14	Postpolio syndrome
G210	Malignant neuroleptic syndrome
G230	Hallervorden-Spatz disease
G231	Progressive supranuclear ophthalmoplegia [Steele-Richardson-Olszewski]
G232	Multiple system atrophy, parkinsonian type [MSA-P]
G241	Idiopathic familial dystonia
G243	Spasmodic torticollis

Code	Code Description
G244	Idiopathic orofacial dystonia
G245	Blepharospasm
G360	Neuromyelitis optica [Devic]
G370	Diffuse sclerosis
G371	Central demyelination of corpus callosum
G375	Concentric sclerosis [BalÃ³]
G404	Other generalized epilepsy and epileptic syndromes
G408	Other epilepsy
G474	Narcolepsy and cataplexy
G50	Disorders of trigeminal nerve
G51	Facial nerve disorders
G52	Disorders of other cranial nerves
G53	Cranial nerve disorders in diseases classified elsewhere
G564	Causalgia
G600	Hereditary motor and sensory neuropathy
G601	Refsum disease
G602	Neuropathy in association with hereditary ataxia
G610	Guillain-Barré syndrome
G700	Myasthenia gravis
G702	Congenital and developmental myasthenia
G710	Muscular dystrophy
G711	Myotonic disorders
G712	Congenital myopathies
G723	Periodic paralysis
G731	Lambert-Eaton syndrome
G735	Myopathy in endocrine diseases
G901	Familial dysautonomia [Riley-Day]
G903	Multi-system degeneration
G912	Normal-pressure hydrocephalus
G950	Syringomyelia and syringobulbia
H185	Hereditary corneal dystrophies
H186	Keratoconus
H351	Retinopathy of prematurity
H494	Progressive external ophthalmoplegia
H810	Ménière's disease
H905	Sensorineural hearing loss, unspecified
I00	Rheumatic fever without mention of heart involvement
I01	Rheumatic fever with heart involvement
I270	Primary pulmonary hypertension
I30	Acute pericarditis
I310	Chronic adhesive pericarditis
I311	Chronic constrictive pericarditis

Code	Code Description
I420	Dilated cardiomyopathy
I424	Endocardial fibroelastosis
I425	Other restrictive cardiomyopathy
I675	Moyamoya disease
I731	Thromboangiitis obliterans [Buerger]
I773	Arterial fibromuscular dysplasia
I774	Coeliac artery compression syndrome
I780	Hereditary haemorrhagic telangiectasia
I81	Portal vein thrombosis
I820	Budd-Chiari syndrome
J632	Berylliosis
J67	Hypersensitivity pneumonitis due to organic dust
K000	Anodontia
K035	Ankylosis of teeth
K220	Achalasia of cardia
K523	Indeterminate colitis
K627	Radiation proctitis
K743	Primary biliary cirrhosis
K754	Autoimmune hepatitis
K765	Hepatic veno-occlusive disease
L100	Pemphigus vulgaris
L101	Pemphigus vegetans
L120	Bullous pemphigoid
L123	Acquired epidermolysis bullosa
L130	Dermatitis herpetiformis
L131	Subcorneal pustular dermatitis
L431	Bullous lichen planus
L440	Pityriasis rubra pilaris
L512	Toxic epidermal necrolysis [Lyell]
L563	Solar urticaria
L630	Alopecia (capitis) totalis
L631	Alopecia universalis
L661	Lichen planopilaris
L681	Acquired hypertrichosis lanuginosa
L722	Steatocystoma multiplex
L813	Café au lait spots
L83	Acanthosis nigricans
L850	Acquired ichthyosis
L88	Pyoderma gangrenosum
L930	Discoid lupus erythematosus
L931	Subacute cutaneous lupus erythematosus
L932	Other local lupus erythematosus

Code	Code Description
L983	Eosinophilic cellulitis [Wells]
M028	Other reactive arthropathies
M061	Adult-onset Still disease
M08	Juvenile arthritis
M111	Familial chondrocalcinosis
M300	Polyarteritis nodosa
M301	Polyarteritis with lung involvement [Churg-Strauss]
M303	Mucocutaneous lymph node syndrome [Kawasaki]
M310	Hypersensitivity angiitis
M313	Wegener granulomatosis
M314	Aortic arch syndrome [Takayasu]
M317	Microscopic polyangiitis
M320	Drug-induced systemic lupus erythematosus
M330	Juvenile dermatomyositis
M331	Other dermatomyositis
M332	Polymyositis
M339	Dermatopolymyositis, unspecified
M34	Systemic sclerosis
M351	Other overlap syndromes
M352	Behçet disease
M354	Diffuse (eosinophilic) fasciitis
M356	Relapsing panniculitis [Weber-Christian]
M411	Juvenile idiopathic scoliosis
M600	Infective myositis
M611	Myositis ossificans progressiva
M722	Plantar fascial fibromatosis
M854	Solitary bone cyst
M911	Juvenile osteochondrosis of head of femur [Legg-CalvÃ©-Perthes]
M932	Osteochondritis dissecans
M941	Relapsing polychondritis
N251	Nephrogenic diabetes insipidus
N301	Interstitial cystitis (chronic)
N856	Intrauterine synechiae
O01	Hydatidiform mole
O903	Cardiomyopathy in the puerperium
P240	Neonatal aspiration of meconium
P271	Bronchopulmonary dysplasia originating in the perinatal period
P702	Neonatal diabetes mellitus
Q000	Anencephaly
Q001	Craniorachischisis
Q002	Iniencephaly
Q01	Encephalocele

Code	Code Description
Q02	Microcephaly
Q041	Arhinencephaly
Q042	Holoprosencephaly
Q045	Megalencephaly
Q05	Spina bifida
Q060	Amyelia
Q062	Diastematomyelia
Q064	Hydromyelia
Q070	Arnold-Chiari syndrome
Q100	Congenital ptosis
Q101	Congenital ectropion
Q102	Congenital entropion
Q112	Microphthalmos
Q120	Congenital cataract
Q121	Congenital displaced lens
Q122	Coloboma of lens
Q123	Congenital aphakia
Q130	Coloboma of iris
Q133	Congenital corneal opacity
Q150	Congenital glaucoma
Q160	Congenital absence of (ear) auricle
Q161	Congenital absence, atresia and stricture of auditory canal (external)
Q163	Congenital malformation of ear ossicles
Q164	Other congenital malformations of middle ear
Q172	Microtia
Q200	Common arterial trunk
Q201	Double outlet right ventricle
Q202	Double outlet left ventricle
Q203	Discordant ventriculoarterial connection
Q204	Double inlet ventricle
Q205	Discordant atrioventricular connection
Q210	Ventricular septal defect
Q211	Atrial septal defect
Q212	Atrioventricular septal defect
Q213	Tetralogy of Fallot
Q214	Aortopulmonary septal defect
Q221	Congenital pulmonary valve stenosis
Q224	Congenital tricuspid stenosis
Q225	Ebstein anomaly
Q226	Hypoplastic right heart syndrome
Q228	Other congenital malformations of tricuspid valve
Q229	Congenital malformation of tricuspid valve, unspecified

Code	Code Description
Q230	Congenital stenosis of aortic valve
Q231	Congenital insufficiency of aortic valve
Q232	Congenital mitral stenosis
Q234	Hypoplastic left heart syndrome
Q240	Dextrocardia
Q241	Laevocardia
Q242	Cor triatriatum
Q243	Pulmonary infundibular stenosis
Q244	Congenital subaortic stenosis
Q245	Malformation of coronary vessels
Q246	Congenital heart block
Q250	Patent ductus arteriosus
Q251	Coarctation of aorta
Q256	Stenosis of pulmonary artery
Q26	Congenital malformations of great veins
Q271	Congenital renal artery stenosis
Q273	Peripheral arteriovenous malformation
Q30	Congenital malformations of nose
Q31	Congenital malformations of larynx
Q320	Congenital tracheomalacia
Q332	Sequestration of lung
Q333	Agenesis of lung
Q35	Cleft palate
Q382	Macroglossia
Q390	Atresia of oesophagus without fistula
Q391	Atresia of oesophagus with tracheo-oesophageal fistula
Q410	Congenital absence, atresia and stenosis of duodenum
Q411	Congenital absence, atresia and stenosis of jejunum
Q412	Congenital absence, atresia and stenosis of ileum
Q418	Congenital absence, atresia and stenosis of other specified parts of small intestine
Q419	Congenital absence, atresia and stenosis of small intestine, part unspecified
Q420	Congenital absence, atresia and stenosis of rectum with fistula
Q421	Congenital absence, atresia and stenosis of rectum without fistula
Q422	Congenital absence, atresia and stenosis of anus with fistula
Q423	Congenital absence, atresia and stenosis of anus without fistula
Q431	Hirschsprung disease
Q442	Atresia of bile ducts
Q446	Cystic disease of liver
Q510	Agenesis and aplasia of uterus
Q511	Doubling of uterus with doubling of cervix and vagina
Q513	Bicornate uterus
Q514	Unicornate uterus

Code	Code Description
Q515	Agenesis and aplasia of cervix
Q550	Absence and aplasia of testis
Q555	Congenital absence and aplasia of penis
Q600	Renal agenesis, unilateral
Q601	Renal agenesis, bilateral
Q603	Renal hypoplasia, unilateral
Q604	Renal hypoplasia, bilateral
Q605	Renal hypoplasia, unspecified
Q611	Polycystic kidney, autosomal recessive
Q614	Renal dysplasia
Q615	Medullary cystic kidney
Q620	Congenital hydronephrosis
Q622	Congenital megaloureter
Q640	Epispadias
Q641	Exstrophy of urinary bladder
Q643	Other atresia and stenosis of urethra and bladder neck
Q673	Plagiocephaly
Q69	Polydactyly
Q70	Syndactyly
Q710	Congenital complete absence of upper limb(s)
Q711	Congenital absence of upper arm and forearm with hand present
Q712	Congenital absence of both forearm and hand
Q713	Congenital absence of hand and finger(s)
Q714	Longitudinal reduction defect of radius
Q715	Longitudinal reduction defect of ulna
Q716	Lobster-claw hand
Q720	Congenital complete absence of lower limb(s)
Q721	Congenital absence of thigh and lower leg with foot present
Q722	Congenital absence of both lower leg and foot
Q723	Congenital absence of foot and toe(s)
Q724	Longitudinal reduction defect of femur
Q725	Longitudinal reduction defect of tibia
Q726	Longitudinal reduction defect of fibula
Q727	Split foot
Q730	Congenital absence of unspecified limb(s)
Q743	Arthrogryposis multiplex congenita
Q750	Craniosynostosis
Q754	Mandibulofacial dysostosis
Q761	Klippel-Feil syndrome
Q770	Achondrogenesis
Q771	Thanatophoric short stature
Q772	Short rib syndrome

Code	Code Description
Q773	Chondrodysplasia punctata
Q774	Achondroplasia
Q775	Dystrophic dysplasia
Q777	Spondyloepiphyseal dysplasia
Q780	Osteogenesis imperfecta
Q781	Polyostotic fibrous dysplasia
Q782	Osteopetrosis
Q783	Progressive diaphyseal dysplasia
Q784	Enchondromatosis
Q786	Multiple congenital exostoses
Q790	Congenital diaphragmatic hernia
Q793	Gastroschisis
Q796	Ehlers-Danlos syndrome
Q801	X-linked ichthyosis
Q802	Lamellar ichthyosis
Q803	Congenital bullous ichthyosiform erythroderma
Q804	Harlequin fetus
Q810	Epidermolysis bullosa simplex
Q812	Epidermolysis bullosa dystrophica
Q821	Xeroderma pigmentosum
Q822	Mastocytosis
Q823	Incontinentia pigmenti
Q824	Ectodermal dysplasia (anhidrotic)
Q830	Congenital absence of breast with absent nipple
Q831	Accessory breast
Q843	Anonychia
Q850	Neurofibromatosis (nonmalignant)
Q851	Tuberous sclerosis
Q860	Fetal alcohol syndrome (dysmorphic)
Q861	Fetal hydantoin syndrome
Q872	Congenital malformation syndromes predominantly involving limbs
Q873	Congenital malformation syndromes involving early overgrowth
Q874	Marfan syndrome
Q90	Down syndrome
Q910	Trisomy 18, meiotic nondisjunction
Q911	Trisomy 18, mosaicism (mitotic nondisjunction)
Q912	Trisomy 18, translocation
Q913	Edwards' syndrome, unspecified
Q914	Trisomy 13, meiotic nondisjunction
Q915	Trisomy 13, mosaicism (mitotic nondisjunction)
Q916	Trisomy 13, translocation
Q917	Patau syndrome, unspecified

Code	Code Description
Q927	Triploidy and polyploidy
Q93	Monosomies and deletions from the autosomes, not elsewhere classified
Q96	Turner syndrome
Q970	Karyotype 47,XXX
Q973	Female with 46,XY karyotype
Q985	Karyotype 47,XYY
Q990	Chimera 46,XX/46,XY
Q991	46,XX true hermaphrodite
Q992	Fragile X chromosome
T572	Toxic effect: Manganese and its compounds
T883	Malignant hyperthermia due to anaesthesia