Metabolic Pathways
Networks of Care

A needs assessment and review of services for people with inherited metabolic disease in the United Kingdom

Public Health Genetics

Hilary Burton

November 2005

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Full Report

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The full report and overview only can also be downloaded from the PHGU website:
www.phgu.org.uk

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Public Health Genetics

Foreword

Metabolic medicine and treatment of patients with inherited metabolic disease is a small but rapidly advancing area of medicine. New methods in biochemical and genetic diagnosis, together with improved treatments have much to offer patients, but it is a challenge to ensure that all have access to specialist management. Developments in newborn screening will give further emphasis to these conditions and highlight any deficiencies in service provision.

A British Inherited Metabolic Disease workshop held in 2002 first gave expression to professional concern that services in the UK would increasingly struggle to meet current and emerging needs. Following presentation of the BIMDG "Service Vision" to the Joint Committee on Medical Genetics, the profession was heartened by our colleagues' recognition that there should be investment in strategic planning for Inherited Metabolic Disease as a group of conditions in the UK. We are grateful to the Joint Committee for taking leadership, for the Department of Health in providing financial support for a series of stakeholder meetings and for Dr Hilary Burton and her team at the Public Health Genetics Unit in Cambridge for taking forward this needs assessment and strategic review.

Since the initial meeting in November 2004, with Dr Hilary Burton`s energy and support from her team in Cambridge, the success of the project has continued to outstrip the BIMDG's high expectations. Professionals and patient groups have worked together to produce a detailed review that brings together scientific evidence on the epidemiology of inherited metabolic disease with a careful assessment of services for patients.

With this report we now have a framework for looking at how we organise our services and a review that can be used to inform Health Commissioners about inherited metabolic disorders and the problems that patients experience. The review provides the impetus for the IMD community to work towards improving the delivery of services, and a focus for our efforts to secure additional resources for the benefit of patients.

We have come a long way since our workshop in Autumn of 2002. On behalf of the BIMDG I thank Dr Hilary Burton and her team from the Public Health Genetics Unit in Cambridge for this major contribution which I hope will ultimately improve the quality of life and outcome for our patients.

Dr Graham J Shortland
Chairman of the BIMDG

October 2005

Summary of policy points

All patients with inherited metabolic disease (IMD) should have access to highly specialist care in which the necessary expert clinical, nursing and dietetic and other support is coordinated with specialist laboratory testing for diagnosis and monitoring. For many, this should be combined with shared care arrangements in which, where appropriate, care is provided nearer home under agreed protocols.

A UK needs assessment and service review undertaken at the request of the Joint Committee on Medical Genetics estimated that there are about 600 new cases per year. Some 10,000 prevalent cases attend specialist services across the UK, but it is likely that a further 6,000 children and 3,000 adults are looked after by local services or lost to follow up. This unmet need will increase as a result of new technologies for diagnosis, more effective treatments and new neonatal screening programmes.

There are major regional disparities in provision across the country, with some regions having little or no specialist service.

Specialist provision needs to be expanded and developed across the UK to provide a comprehensive and more equitable service to the population. The prime strategic elements to achieve this are:

- A UK wide formal strategic advisory group to maintain an overview and guide strategy implementation
- Formal and explicit commissioning arrangements for IMD that reflect the need to generate critical mass of patients to support comprehensive service provision balanced with reasonable geographic accessibility
- Continued strengthening of biochemical laboratory services, maintaining integration with clinical services and with molecular and cytogenetic laboratories, and including training and manpower, provision of equipment, and safeguarding of highly specialist tests
- Reconfiguration of specialist clinical services through development of networks that ensure: access to a complete clinical team including doctors, nurses, dietitians and, where possible, psychologists; emergency cover on a 24 hour basis; formal arrangements with other supporting specialties; and longer term robustness and continuity.
- Development by networks of formal supporting arrangements on a regional basis, including as appropriate: outreach; shared care; education and support for other health professionals
- Robust manpower planning, resources and development for formal training for all involved specialties on a UK wide basis. Development of courses in IMD at Masters level for dietitians and nurses
- Support and close work with voluntary groups to assist them in providing information about specialist services to their members and participate in education for health professionals and patients

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Section One Overview

1 Overview and recommendations

Purpose

The importance of specialist care for people with inherited metabolic disease (IMD) is increasing as new technologies enhance our ability to screen for, diagnose and provide effective treatments. Yet in the UK the services have not evolved to fulfil these needs in a way that is comprehensive, high quality and equitable for all the population. In this report we present an assessment of population need, and a review of current specialist provision in the UK, which together provide a baseline on which an improved system of care can be built. As a result of discussion with stakeholders, both within the professions and from voluntary organisations, we make recommendations to service providers and to commissioners at all levels on the key strategies that will be important for service change.

The report is structured as an overview with main recommendations, followed by separate chapters which provide details of work undertaken and evidence.

We hope that the report will prove the beginning of a process that will lead to real health benefits for patients and their families, and to the emergence of a mature, exciting and professionally satisfying subspecialty for health professionals.

Introduction

IMDs are a group of over five hundred conditions, each caused by deficient activity in a single enzyme in a pathway of intermediary metabolism. They lead to severe disruption of metabolic processes in the body, such as those concerned with energy production, manufacture or breakdown of proteins, and management and storage of fats and fatty acids. The result is that patients have either a deficiency of products essential for health or, sometimes, an accumulation of unwanted or toxic products. This can mean disease or damage in many organ systems, and many of these conditions lead to severe learning or physical disability and death at an early age. Phenylketonuria (PKU), a condition for which testing is possible at birth, is a typical example of an IMD.

IMDs are thus a diverse range of conditions, which vary widely in their presentation and management according to which body systems are affected. They may sensibly be viewed as a specialist care group, however, on a number of counts:

- they require a wide set of specialist biochemical and molecular tests for diagnosis and subsequent monitoring
- patients need care from a specialist multi-disciplinary team experienced in diagnosis, management and prognosis
- they are multi-system and involve coordination of input from a great many clinical specialties
- they are inherited diseases and have implications for family members, requiring the input of specialist genetic services
- patients may need specialist therapies such as enzyme replacement therapies (ERTs) or special diets
- they are chronic diseases, and patients and their families may need a wide range of care and support from health services and other agencies, including the voluntary sector, throughout their lives.

Background

In January 2004 Dr Graham Shortland (Chairman of the British Inherited Metabolic Disease Group (BIMDG) and Consultant Paediatrician at Cardiff) and Dr Philip Lee (Consultant in Metabolic Medicine, University College Hospital, London) presented work by the BIMDG on IMD services in the UK to the Joint Committee on Medical Genetics. They highlighted professional concerns about services, particularly with respect to the clinical workforce, and made proposals for service developments. These were set out in the BIMDG document A Service Vision and Standards of Care[i]. After further consultation within the Committee and with parent groups including the Royal College of Pathologists, the Joint Committee for Higher Medical Training and The Royal College of Physicians, it was agreed that the Joint Committee on Medical Genetics would take leadership in calling a high-level meeting of key stakeholders to initiate a detailed examination of the current problems with the service and to propose possible solutions. The Department of Health provided financial support for this review. The Public Health Genetics Unit (PHGU) in Cambridge agreed to take this work forward as part of their 2005/6 work programme.

Method

The work was led by Dr Hilary Burton, Consultant in Public Health Medicine at the PHGU. A stakeholder group provided expertise and guidance throughout the development of the project, giving the viewpoints of the professionals involved in service provision, voluntary groups, service commissioners and workforce experts, as well as ensuring representation and involvement from England, Wales, Scotland and Northern Ireland. The PHGU provided expertise in epidemiology, needs assessment and service review, as well as the organisation and administration of the programme (see Appendix 1 for membership of the stakeholder group).

The stakeholder group met four times between November 2004 and October 2005. Special meetings were also held with representatives of voluntary organisations, and with groups of specialist nurse and specialist dietitians. The stakeholder group obtained and assembled evidence through work undertaken by various individual members and by epidemiologists and others at the PHGU: clinicians developed case histories that illustrate agreed aspects of the complexity of specialist work undertaken by doctors, nurses, dietitians and laboratory services; Professor Anne Green, the Lead Scientist for the National Metabolic Biochemistry Network, undertook a review of laboratory services; members of the PHGU undertook reviews of the epidemiology of IMDs and specialist commissioning mechanisms and their use in IMD services (Dr Simon Sanderson), and a review of the organisation and provision of specialist services throughout the UK (Dr Hilary Burton).

In July 2005 the main findings and provisional recommendations were presented to the Annual General Meeting of BIMDG at their conference in Birmingham. This was followed up by circulation of a report to members in the BIMDG Newsletter, inviting them to review draft documents, contribute further evidence or comment on findings or recommendations.

Main findings

Epidemiology

There are over five hundred known IMDs – a number that is increasing as our knowledge of human metabolism advances and our ability to undertake tests develops. Although each condition is rare, it is usually estimated in the worldwide literature that IMDs occur in 1 in 2,500 to 5,000 live births (though the basis of this figure is not clear). In the UK, with an average of 793,000 live births a year, this would suggest about 300–600 cases in the newborn population each year, though newer figures from our own work suggest that the number may be higher. The most common conditions are those of amino acid metabolism (e.g. PKU), organic acid metabolism, disorders of fatty acid

oxidation (e.g. MCADD), lysosomal storage diseases (LSDs; e.g. Gaucher disease, Fabry disease), and disorders of urea cycle, carbohydrate metabolism and mitochondria.

The majority of IMDs present in childhood and, for some disorders, few patients survive into adulthood. A report published in 2002[ii] estimated that this figure is about 11 per cent, although the number is increasing as a result of earlier detection (e.g. through expanded neonatal screening programmes) and improved treatment (including specific replacement therapies, such as Cerezyme for Gaucher disease). This has implications for the planning and provision of services for adult patients with IMD.

There are very few epidemiological data specific to the UK, and virtually none on prevalence or survival, except in a few highly selected conditions. Available international and national data need to be interpreted carefully as there are a large number of problems in ascertaining, classifying and coding IMDs, especially for those with variable clinical presentations. In the UK the lack of a national register of patients with IMDs significantly hampers clinical research and practice and the planning, procuring and monitoring of services for patients with these conditions. This will become particularly important as clinical trials of new treatments are needed.

As a result of new research conducted in the West Midlands, we have estimated that the incidence is nearer to 1 in 1,000. Our estimated annual incidence ('birth prevalence') for the UK based on these data is given in Table 1.1. (See Chapter 2 for further consideration of assumptions made in estimates of birth prevalence).

Table 1.1 Incidence of IMDs in the West Midlands, based on number of new diagnostic test results

Condition	Five-year average number of cases	Birth prevalence per 10,000 live births	Number needed to diagnose one case	*Upper 95% ci*	*Lower 95% ci*
PKU	5.00	0.81	12420	5008	33784
Other amino acid	11.60	1.87	5354	2943	9990
Urea cycle defects	2.80	0.45	22179	6702	90909
Carbohydrate	3.80	0.61	16343	4509	52910
Organic acid	7.80	1.26	7962	3837	17301
Glycogen storage	4.20	0.68	14786	5504	44643
Lysosomal storage	12.00	1.93	5175	2874	9551
Purine and pyrimidine†	0.80	0.13	77628	12063	2000000
Fatty acid oxidation	4.80	0.77	12938	5123	35971
Peroxisomal	4.60	0.74	13500	5244	38462
Mitochondrial	12.60	2.03	4929	2776	8953
Metals‡	2.20	0.35	28228	7418	147059
Lipids and steroids#	4.00	0.64	15526	5647	48544
Porphyrin and haem*	1.00	0.03	310510	10070	3333333
Miscellaneous	2.80	0.45	22179	6702	90909
Total	**79.20**	**12.8**	**784**	**619**	**970**

† Incomplete as diagnosis usually made in super-specialist centres.
‡ Incomplete as some diagnoses will be made in non-specialist laboratories.
 # Includes only steroid sulphatase disorders and Smith-Lemli-Opitz syndrome.
** Incomplete as diagnosis usually made in super-specialist centres.*

Source - Green and Preece, Birmingham Children's Hospital NHS Trust 2005.

It can be seen from this that the expected birth prevalence is higher than previous estimates; based on West Midlands data collected over a five-year period, we estimate that birth prevalence is 1 in 784 live births (95% *ci* 1 in 619 to 1 in 970).

The specialised nature of services

Specialist services for IMD aim to provide more effective and higher-quality services. The expected outcomes in terms of effectiveness include these:

- Decrease in mortality
- Decrease in morbidity
- Reduction in disability
- Prevention of harm to family members
- Prevention of damage to unborn child
- Reproductive choice
- Overall quality of life (reduction of handicap).

These are discussed further in Chapters 3 and 11, along with a consideration of structural and process aspects of services expected to be required to deliver improved outcomes.

We were unable to find UK or international evidence for aspects of services as a whole that lead to better health outcomes across the range of IMDs. The group therefore sought to illustrate the ways in which specialist IMD practice can improve outcomes for patients and their families. The full case histories are given in Appendix 3 and in the reviews of specialist nursing and dietitian roles. Names have been changed.

Difficulty of diagnosis and complexity of management across different disciplines and specialities (case histories 1 and 2)

The first case is of an 11-year-old with methylmalonic acidaemia (MMA) who presented several times in the first few weeks of life with poor feeding, intermittent vomiting and lethargy, and at later stages with drowsiness. However, it was not until he was seen by a doctor who had experience of IMD that contact was made with the regional specialist IMD service and appropriate investigations to diagnose MMA were undertaken. At this stage he was encephalopathic and required major intensive care support, including ventilation and haemfiltration. He made a gradual recovery and was placed on a therapeutic diet, but remained neurologically impaired. His management since has required continued and regular input from a large number of professionals. These include the specialist IMD team (medical, genetic, dietetic, psychology, laboratory); other specialist services (renal, surgical, orthopaedic, gastroenterology); community (medical, physiotherapy, occupational therapy, nursing, social services); and educational (psychology, special educational needs).

A further example of difficulty in diagnosis owing to variable presentation in the older patient is given in case history 2, where failure to recognise medium chain acyl CoA dehydrogenase deficiency (MCADD) in a young adult led to an avoidable death.

Meticulous long-term follow-up to prevent harm to unborn child (case history 3)

Case history 3 describes two contrasting patients with PKU. In the first, the patient was lost to follow-up in her teenage years. Though well herself, she presented with a severely brain-damaged son. By contrast, a second woman was followed up meticulously, with planned transfer from child to adult services. She was restarted on a phenylalanine-restricted diet shortly before pregnancy, monitored throughout pregnancy and gave birth to a healthy baby daughter, whose developmental and IQ assessment documented up to age 8 years were normal.

The need for a multi-disciplinary team (case history 4)

Ornithine carbamyl transferase (OCT) deficiency is an X-linked urea cycle defect that causes high blood levels of ammonia and can lead to severe brain damage and early death. Management requires close collaboration of specialists in IMD and others. The IMD team at one centre looked after a 19-year-old patient who presented with an advanced pregnancy and required genetic counselling and antenatal diagnosis for the fetus. Though, as in this case, the manifestations in women are usually relatively mild, the specialist team knew from previous reports that the stress of childbirth could suddenly lead to potentially fatal high levels of ammonia. They also knew that the disease is often fatal in males in the first year of life, so it would be important to offer this woman antenatal testing.

In this case, molecular diagnosis showed that the fetus was male, and affected with the condition. The patient chose to have a late termination of pregnancy, and during this procedure needed frequent and detailed close monitoring by the biochemical and dietetic teams over the first 24–48 hours after delivery as well as very careful liaison with the obstetric team, with the renal unit ready to undertake emergency dialysis if necessary.

Managing familial aspects (case history (e) in Chapter 7)

Specialist nurses described the case of a 43-year-old man diagnosed with Fabry disease following finding protein in his urine and subsequent discovery of renal damage and cardiac involvement. Three asymptomatic sisters required counselling and screening, and two were found to be carriers. With knowledge of the family history, a nephew who had presented with a stroke at age 41 was also found to have the disease and his family was also counselled.

Managing the acutely ill neonate through specialist diet (case history (a) in Chapter 8)

Dietitians described a typical case of an 11-day-old boy presenting with encephalopathy and diagnosed with Maple Syrup Urine Disease. He required management in the intensive care unit (ICU) in a tertiary metabolic unit, where he underwent ventilation and dialysis, and he was put on a special diet with restricted branch chain amino acids tailored and correctly balanced to restore biochemistry gradually to normal. This would become a lifelong diet, with parents trained to institute intensive dietary regimes every time he became unwell.

These case histories illustrate the need for highly specialised services and what can be achieved by specialist multi-disciplinary teams in services with established systems and connections.

Review of services in the UK

A questionnaire review was undertaken of all clinical services identified as providing specialist IMD care. Twenty-four clinical services provided information to the review; this represented a response from every known service in the UK. There were eighteen service providers in England, one in Wales, four in Scotland, and one in Northern Ireland. However, the degree to which they provided a comprehensive service to a regional population was highly questionable. Full details of the review are given in Chapter 5.

A further review, of specialist porphyria services, was undertaken by Dr Michael Badminton and colleagues and is presented in Chapter 6.

Assessment of need

A total of 10,046 patients were identified as receiving specialist care; 6,547 (63 per cent) children and 3,499 (37 per cent) adults. This represents a UK rate of 16.9 per 100,000 total population. The Northwest is the only UK region set up to provide comprehensive services to a regional

population. The rates for patients attending specialist services here are 82 per 100,000 children and 15.2 per 100,000 adults. If this rate were applied to the UK population as a whole, we should expect a total of approximately 12,100 children and 6,800 adults to be in contact with services. Thus we can estimate a shortfall of some 5,600 children and 3,300 adults with IMD who are not in contact with specialist services.

Service provision

Providers of IMD services are spread throughout the UK, with the exception of the East Midlands, where there are no services. **However, the degree to which they provide comprehensive services is highly variable.** Table 2.1 gives an outline of providers identified arranged by health service region.

Table 2.1 Outline of services provided on a regional basis

Region	Services identified
Northeast	Royal Victoria Infirmary, Newcastle upon Tyne School of Clinical Medical Sciences, Newcastle upon Tyne
Northwest	Manchester Lysosomal Storage Disorder Service Manchester Willink Biochemical Genetics Unit Royal Liverpool Children's Hospital, Alder Hey
Yorkshire and Humber	St Luke's Hospital, Bradford Northern General Hospital, Sheffield Sheffield Children's NHS Trust Leeds General Infirmary
East Midlands	No services identified
West Midlands	Birmingham Children's Hospital
Eastern	Cambridge University Teaching Hospital (Addenbrooke's Hospital)
London & Southeast	London Guy's Hospital London Royal Free Hospital London Great Ormond Street Hospital for Children London University College Hospital
Southwest	Bristol Royal Hospital for Children North Bristol NHS Trust, Southmead Hospital
Wales	University Hospital of Wales, Cardiff
Scotland	Royal Hospital for Sick Children, Edinburgh West of Scotland Royal Hospital for Sick Children, Glasgow Royal Aberdeen Children's Hospital Ninewells Hospital and Medical School, Dundee
Northern Ireland	Northern Ireland Regional Services for Inherited Metabolic Diseases, Royal Group of Hospitals Trust, Belfast

There are two specialist porphyria services, based at Cardiff and London King's College Hospital. Both are recognised by the Supra Regional Assay Service centres offering expert analysis, clinical interpretation and consultative clinical back-up. There are a further small number of regional units, where a more limited range of porphyrin biochemistry tests are offered and there is some clinical service. Examples include services in Bedford, Belfast, Dundee, Leeds and Salford.

Regional services

Six services – namely London Guy's, London Great Ormond Street (GOSH), Manchester, Birmingham, Cambridge and Belfast – offer a regional service. Sheffield provides an adult service to a subregional geographical area in South Yorkshire but with a limited whole-time equivalent (WTE) medical time. The same was true of the Newcastle services. Cardiff provides a service mainly to Mid and South Wales, and Scottish services to defined subregions. Otherwise centres tend to serve a more local population around the teaching hospital and are not set up to provide a service to the wider region.

Regional provision is reflected in the commissioning arrangements where Cambridge, Birmingham and Belfast services were commissioned through regional specialist services mechanisms and Sheffield through a commissioning consortium.

Provision for children and adults

There was a greater availability of paediatric services than adult services, and in only seven services were there either joint paediatric/adult services or close coordination of the two, with formal transfer of patients from child to adult services. In many paediatric services, adults continued to attend clinics or sometimes disappeared from the services altogether because there was nowhere to which they could be referred.

Clinical workforce

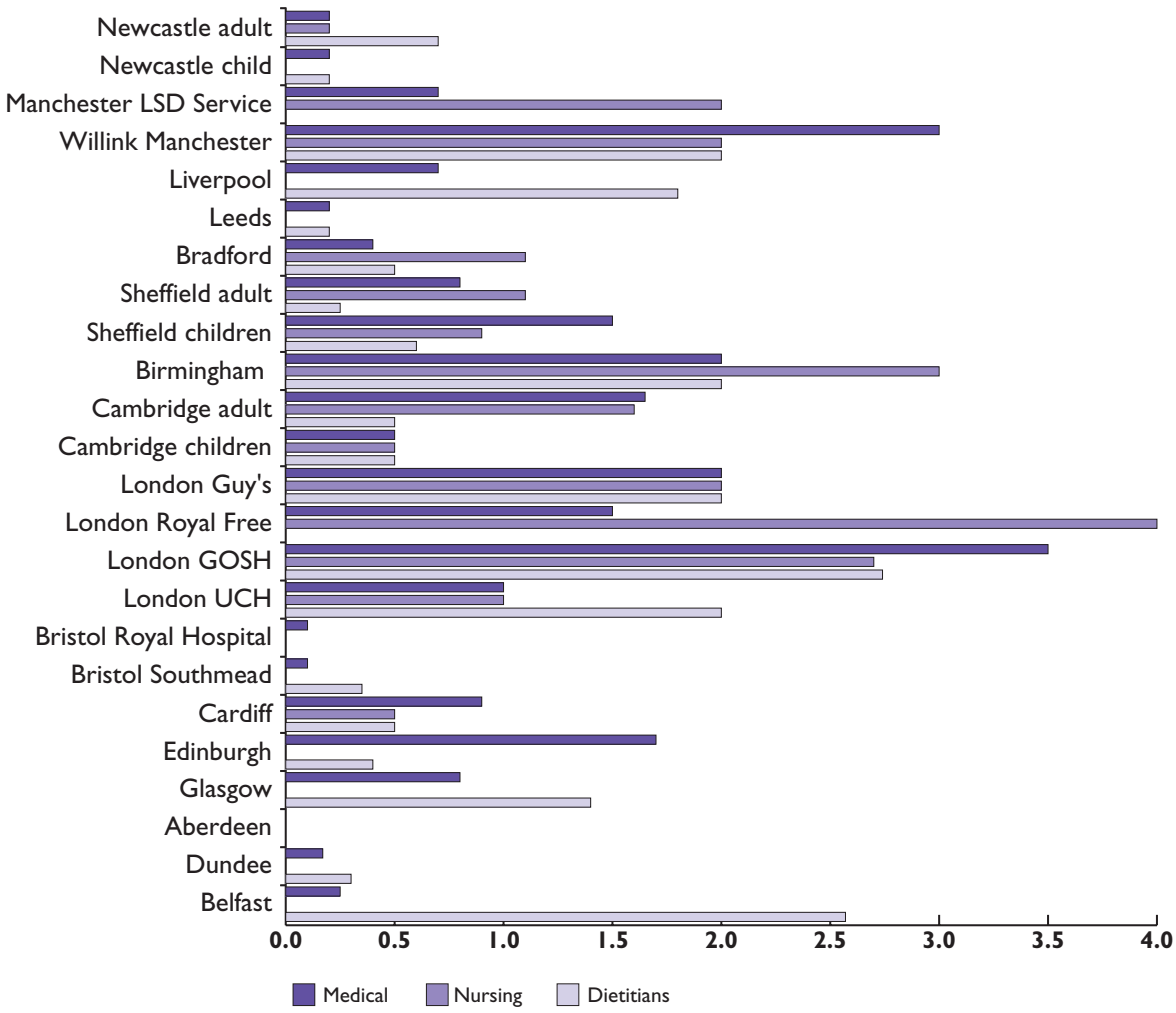
The total workforce is:

- 46 medical consultants (24 WTE)
- 29 nurses (23 WTE)
- 35 dietitians (22 WTE)

(For laboratory workforce see Chapter 4.)

Outside London, there are many medical consultants involved in IMD for whom this is a small proportion of their work. These are a potential source to increase the workforce rapidly. Figure 1.1 gives a summary of the multi-disciplinary team members available in each service.

Figure 1.1 Clinical workforce in IMD (WTE)



There are only five services where there is a full multi-disciplinary team with at least one WTE for each medical, nursing and dietetic staff (Manchester Willink, Birmingham, London Guy's, London GOSH and London UCH).

In addition, a further 19 trusts provide some elements of service, in some cases extremely limited. For example, for nine trusts the total WTE medical input is less than 0.5. The clinical workforce is thus thinly spread across the UK.

IMD patients require input from a specialist multi-disciplinary team including at least medical, nursing and dietetic input integrated closely with the specialist biochemical laboratory team. It is also important that there is 24-hour access to emergency advice to cope with acute diagnostic problems and patients in crisis. Much of this cover is provided by individual goodwill and informal arrangements, sometimes across considerable distances. Only two centres (Manchester Willink and London GOSH) have sufficient medical staff to provide even a modest rota from their own staff. However, across the country it was notable that some consultants were willing to undertake more sessions in IMD if these services could be funded, and so it is clear that extra expert clinical capacity is available to be commissioned.

Out-patients

Available clinic time was very limited for many services. In only fourteen of the services was the total more than one session per week and only seven services provided four or more sessions per week. Thus available clinic time proves a major constraint on the numbers of patients who can be seen and there are particularly long waits in some centres for tertiary referrals and follow-up appointments.

Integration with other specialist services

IMD services need to be closely integrated with a wide range of other specialist services. Some 16 specialties were mentioned as needing formal links. Major IMD centres had joint clinics, joint clinical and pathology meetings, and input from named consultants. In other services this was less formalised – though, as most were in major teaching centres, the opportunity for referral of patients to specialist services was usually available.

Trends, pressure and unmet need

Centres described increasing pressure on services. Some were able to document this in rising numbers of patients known to the service or increasing numbers of referrals. For example, the Willink Centre at Manchester documented a 66 per cent rise in annual numbers of new referrals since 2000. Others noted more patients being referred as new consultants were employed or new services developed. It was also noted that more new diagnoses were being made through the current pilots of extended newborn screening and that this might accelerate as pilot sites were followed by implementation across the country. Numbers of adults attending specialist services have also increased as more children survive into adulthood and new treatments such as enzyme replacement therapies become available.

Services expressed considerable unmet needs. These include over eight hundred adults looked after in paediatric clinics, patients lost to follow-up or turning up in crisis, lack of full multi-disciplinary teams and psychology input, long waits for attendance at clinics and difficulties providing adequate care and follow-up, leading to poor compliance and control. Services were also unable to develop and support peripheral services in local district general hospitals (DGHs) or to support families in the home environment. Lack of resources meant that they could not provide sufficient professional education or be proactive in developing protocols, reviewing services and developing new ones and undertaking audit.

Provision of comprehensive services

A total of 24 providers of IMD services were identified across the UK. However, the degree to which they provide comprehensive services is highly variable. (The Manchester lysosomal service only provides national specialist services for these conditions and so is not included further in this analysis). Following discussion in the stakeholder group, Table 1.3 shows some of the critical criteria for a comprehensive service, listed with a point rating according to the degree to which each criterion was met. The criteria were grouped into broadly clinical (maximum 24 points) and broadly organisational (maximum 6 points). Individual services were then scored against these criteria, and the results are given in Table 1.4.

Table 1.3 Key to rating factors

Clinical areas (maximum 24 points)	Description	Rating
Specialist **workforce**	At least 3 WTE medical staff	***
	At least 3 individuals involved in the provision of medical care	***
	At least 1 WTE each of medical, nursing and dietitian	**
	Complete multi-disciplinary team	*
Number of **out-patient clinics**	More than 4 per week	**
	1–4 per week	*
Involved in provision of coordinated **adult/paediatric** services	Dual provision or involved in formal arrangements	***
	Informal arrangements	**
	Paediatric clinics also provide some care for adults	*
Integration of **laboratory** service	Totally integrated service with multi-disciplinary team meetings at least weekly	***
	Regular formal multi-disciplinary team meetings involving laboratory but less than weekly	**
	Good working relationship but not formalised	*
Outreach services or shared care arrangements	Formal arrangements	***
Links with other **specialist** services	Extensive and formalised	***
	Limited formal arrangements	**
	As required	*
Number of patients	700 or more	***
	200–699	**
	50–199	*
Able to provide information on **disease categories**	Yes	**
	Limited	*
Undertaking **audit** in IMD	Yes	*
Organisational areas (maximum 6 points)		
Geographical provision	National or provision of a regional service	***
	A wider defined geographical population (e.g. a number of PCT areas)	**
	Provision to local population	*
Formal **commissioning** arrangements	National or regional specialist commissioning	***
	Commissioned under other formal arrangements	**
	Commissioning under discussion	*

Overview and Recommendations

Table 1.4 Overview of services

	CLINICAL PROVISION									ORGANISATIONAL		
Centres	**Workforce**	**OP clinics**	**Adult/ paediatric**	**Lab. links**	**Specialist links**	**Number of patients**	**Outreach**	**Disease categories**	**Audit**	**Geographic**	**Commissioning**	**Total (30)**
Newcastle children			**	**No info**	*	*	***			**		**9**
Newcastle adult	*		**	***	***	*		**	*	**	*	**16**
Manchester Willink	****	**	***	***	***	***	***	**	*	***	**No info**	**27**
Liverpool		**No info**	***	**No info**		**				**	**No info**	**7**
Leeds				***	*	*				**		**7**
Bradford	*		*	*	**	*		**		*	*	**10**
Sheffield adult	***	*	***	**	***	*	***			*	**	**19**
Sheffield children	*	*	***	***		*	***	*		**	***	**18**
Birmingham	***	**	*	***	***	***		*	**	***	***	**23**
Cambridge children	*	*	***	**	***	*	***		*	***	***	**21**
Cambridge adult	***	*	***	**	***	**	***		*	***	***	**24**
London Guy's	**	**	***	***	***	**	***	**	*	***	***	**27**
London Royal Free		**	***	***	***	*	***	**	*	***	***	**22**
London GOSH	****	**	***	***	***	***	***	**	**No info**	***	**No info**	**26**
London UCH	**	**	***	*	***	***	***	**	*	***	***	**26**
Bristol Royal				*	**					*		**4**
Bristol Southmead			***	*	*	*		*	*	*		**9**
Cardiff	*	*	***	**	**	**		*	*	**	*	**16**
Edinburgh	***	*		**	**	*		**	*	**		**14**
Glasgow		**	***	***	*	***			*	**		**14**
Aberdeen				**No info**				**		**		**4**
Dundee			***	*	*	*	***		*	**		**12**
Belfast		*	***	***	**	***		*	*	***	***	**20**

Manchester Willink and London GOSH are the only centres that achieve the full rating for comprehensive clinical services in UK. (These centres lost points only because they could not, or did not, provide information on commissioning processes for the services.)

Out of the maximum of 30 points, services may be grouped as follows:

21–30 Manchester Willink, Birmingham; Cambridge (children and adult), London Guy's, London Royal Free, London GOSH, London UCH

11–20 Newcastle (adult), Sheffield (adult and children), Cardiff, Edinburgh, Glasgow, Dundee, Belfast

0–10 Newcastle (children; very little information was provided), Leeds, Bradford, Bristol Royal, Bristol Southmead, Aberdeen.

The following regions did not have a service in the top category: Northeast, Yorkshire and Humber, Southwest, Scotland, Northern Ireland. Apart from East Midlands, where there was no service, the region with the most deficient service was Southwest, where services rated only in the lowest category.

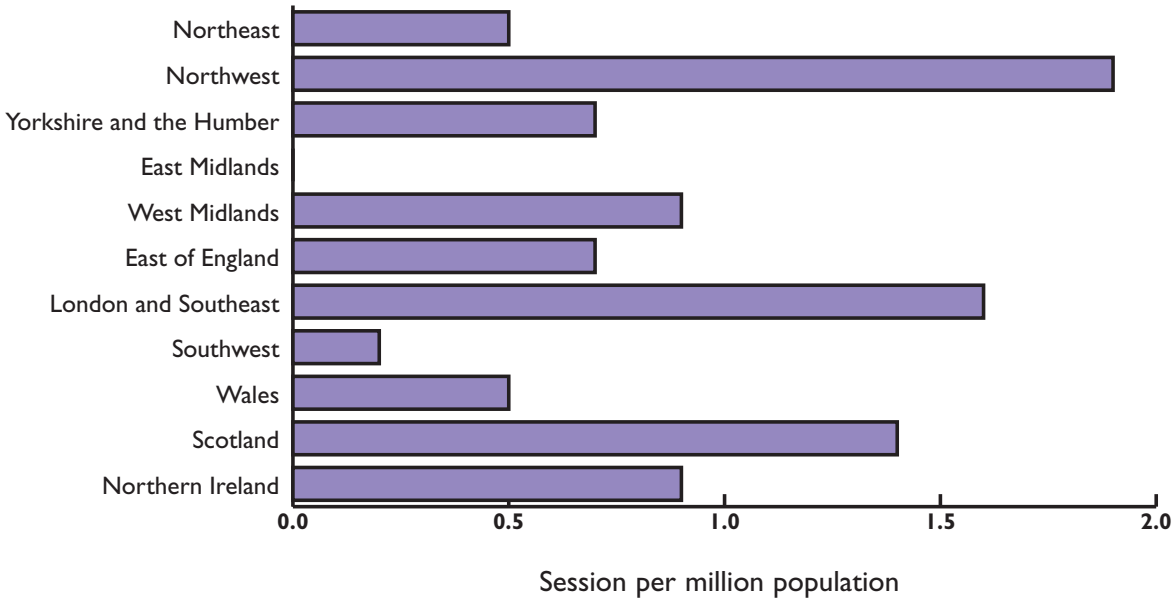
Regional variability in provision

The provision of services across the health regions in England and in Wales, Scotland and Northern Ireland was compared on three parameters in relation to resident population size: provision of out-patient sessions, total clinical staffing, and numbers of patients attending services. It should be noted that these comparisons do not take any account of different needs arising from different disease burden, such as may arise due to the impact of ethnicity and rates of consanguineous marriage. Appendix 4 gives details of resident populations and sources.

Out-patient sessions

The total average weekly provision of out-patient sessions varies widely across the UK regions, with an almost ten-fold variation from 0.2 sessions per million population in the Southwest to 1.9 in the Northwest region (see Figure 1.2).

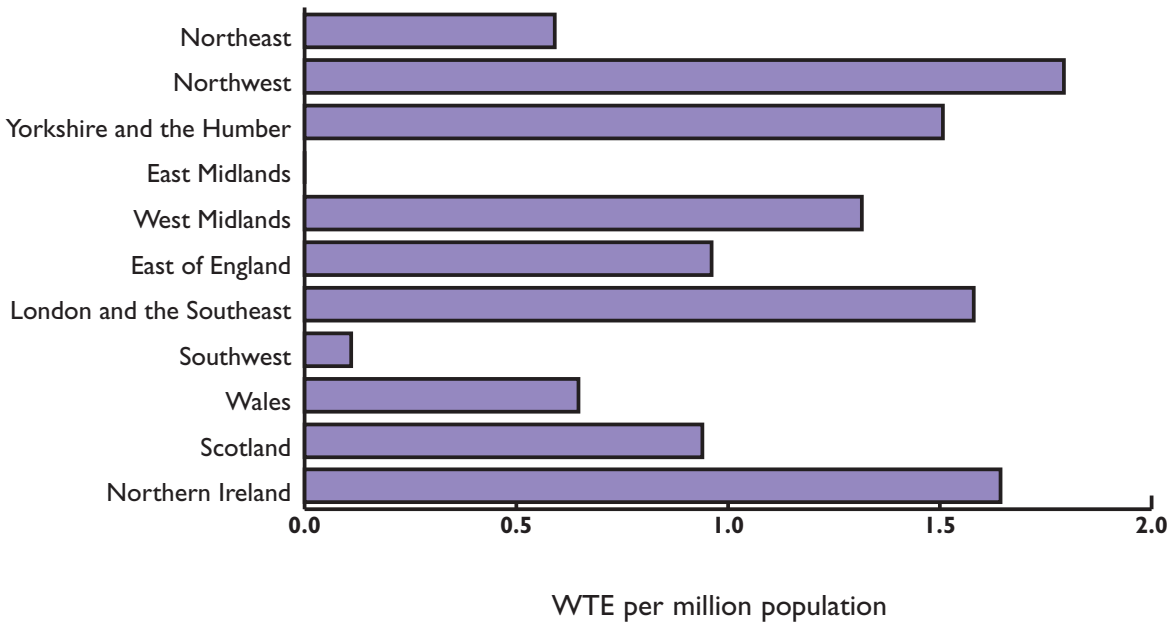
Figure 1.2 Average total number of out-patient sessions per week per million population by region



Clinical workforce

Comparison of total staffing in geographical regions shows huge disparity across the UK (see Figure 1.3). The total clinical staff per million population varies from 0.11 in the Southwest to 1.8 in the Northwest.

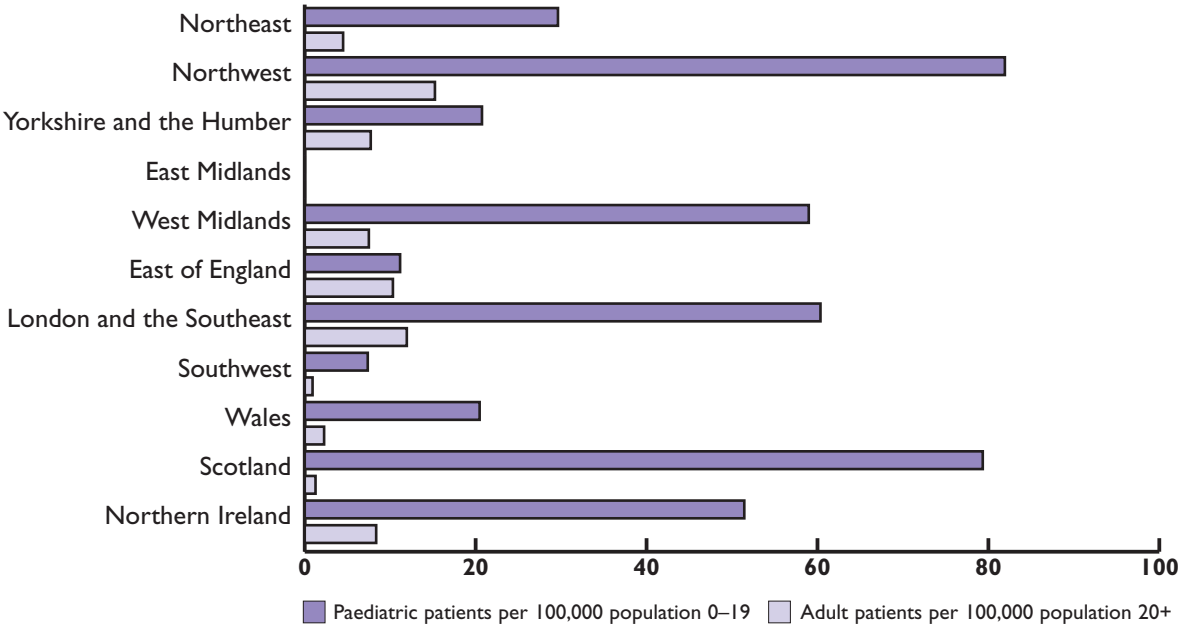
Figure 1.3 Total clinical workforce (WTE per million population) by region



Total numbers of patients attending services

Regional rates of patients attending specialist centres were calculated based on Government Office regions in England and Wales and population statistics for Scotland and Northern Ireland. The population group for child was 0–19, as children with disabilities are often included in paediatric services up to that age. Rates varied from 82.0 per 100,000 child and 15.2 per 100,000 adult in the Northwest to 7.4 per 100,000 child and just under 0.9 per 100,000 adult in the Southwest. (Note that some of the patients from the Southwest and other services may be attending London services and other major centres.) Comparative regional rates are shown in Figure 1.4.

Figure 1.4 Number of patients attending specialist services per 100,000 population by region



Laboratory review

Specialist laboratories play a key role in the diagnosis and management of patients with IMD. The laboratories work together as a formal National Metabolic Biochemistry (Biochemical Genetics) Network across 17 laboratories. The laboratory review was led by Professor Anne Green, Lead Scientist for the Network. It was based on two surveys: a review of service provision undertaken by questionnaire of laboratory services in October to December 2003, and a survey to obtain data on laboratory diagnoses undertaken in February 2005. In the 2003 survey information was sought on current workload patterns, developments and future needs, and robustness of service. There was a 100 per cent response (i.e. all 17 stakeholder laboratories responded; 16 provide the core services whilst one at the Royal Manchester Children's Hospital provides specialist tests only). The survey provides data on workforce, equipment, accommodation and training. In the 2005 survey on diagnoses, information was provided by 13 laboratories. There are no data on diagnoses from Liverpool or Southampton.

Test provision and repertoire

A survey of the number of requests for core tests received by laboratories showed correlation with size of population served. Thus there was no evidence of significant underprovision or overprovision. However, there is a deficiency of acyl carnitine services (required in the investigation of fatty acid oxidation) for some laboratories.

Some of the more specialist tests are vulnerable and a robust service is currently not provided. The Metabolic Biochemistry Network is addressing this issue, but there are concerns about the potential impact of foundation hospitals on provision of the expensive very rare tests.

Turnaround times

Turnaround times for routine core tests are significantly compromised in about 30 per cent of cases by limited staff time and/or equipment shortage or failure.

Out-of-hours services

There are no formal arrangements for emergency out-of-hours work, and *ad hoc* services are dependent on individuals being available and willing. There is a need for more formal back-up arrangements between laboratories in order to provide a full emergency service.

Accommodation for the next five years

Services assessed that laboratory accommodation was adequate at present for 12 out of 14 (86%) services and offices for 8 out of 14 (57%) offices. However, it was anticipated that this would not be sustained, and within the next five years accommodation would become inadequate for 55 per cent of the laboratories and 75 per cent of the offices. This will be particularly important to address as plans are developed for extended newborn screening.

Equipment

Urgent replacement is required for five (30%) Amino Acid Analysers and a further ten will be required in the next three years. Four Tandem Mass Spectrometers will be needed and nine Gas Chromatograph / Mass Spectrometers (50%) nationwide.

Staffing, training and workforce planning

There is close integration between the service laboratory staff and the clinical professionals, with consultants and principal scientists an essential part of the multi-disciplinary team. There is a newly established (2004) higher-specialist training programme for clinical scientists with pump-priming funding from the Department of Health Genetics White Paper. Biomedical scientists train on the job, and there is a requirement for a formal scheme with establishment of training posts.

There are currently a total of 71 scientists in laboratories across the UK, including 22 consultants (medical and scientists), 24 principal scientists and 25 senior scientists. A study undertaken by the Workforce Review Team in May 2004, which included planning for newborn screening developments, estimated that over the next five years there would be a need for an intake of a further 49 trainee clinical scientists and 46 biomedical (senior) scientists to take account of retirements, new posts for developments and training demands, as well as allowing for attrition.

Diagnoses by laboratories

A total of 573 diagnoses were made in 2003/4 by the 14 laboratories responding to the 2005 survey. Taking into account the populations served by these laboratories, this amounts to an average rate of around 9.5 per million annual diagnoses. When extrapolated to the UK population, it is estimated that there would be around 550 new cases per annum. Nearly 75 per cent of new diagnoses were in children under 10 years, and approximately 20 per cent of cases were in adults over 16 years.

For many patients there are no specialist clinical services to which referral may be made.

Specialist nursing

An experienced nurse plays an important role in the multi-disciplinary team for IMD. The work is highly specialised and involves complex aspects of care for individual patients, as well as working on familial aspects of disease with the extended family. In addition to direct clinical work with families, specialist nurses also take on roles within the organisation such as leading clinics, providing first-line telephone information and advice, undertaking teaching, coordinating services, research and becoming involved in commissioning.

The specialist role of the nurse within the multi-disciplinary team is thus well recognised, and it is of concern that nurses were only included in 14 of the 24 services. Of further concern is that there is no formal nurse training for IMD; most practitioners have simply learned on the job, sometimes with an initial small amount of training as part of their induction. They then go on to have further training through ward rounds and attendance at various educational meetings. Support to nurse education is provided through the nurses' network of the BIMDG.

Formal and accredited education for nurses in IMD is urgently needed, and should be at basic level as an introduction and at a more specialist level. It should cover clinical aspects, pathophysiology, genetics, biochemistry, dietetics, social and psychological aspects, research and development aspects, as well as the nursing role in providing support for patient and family.

As a preliminary to this, key competencies should be set out on a national basis and courses should be recognised and accredited.

As an adjunct, nurses' professional development should be supported through grants to enable attendance at national and international meetings, seminars and workshops. One example is that the annual Gaucher course at the Royal Free Hospital, currently offered to physicians from other countries, could be offered to nurses from Europe too.

Specialist dietetics

An experienced dietitian plays an important role in the multi-disciplinary core team for IMD. The work is highly specialised and complex. Good dietary management is crucial to the outcome in many IMDs.

The specialist dietitian leads and is responsible for the individualised dietary management of children and adults with IMD. This involves formulating the diet and teaching patients, parents, carers and other relevant lay persons about the patient's dietary treatment. The dietitian provides support and collaborates with smaller specialist units and DGHs, providing expert advice and education to medical, nursing and allied health professionals. In addition, the dietitian will provide advice and support on the dietary management of patients with IMDs to other professionals in health, social care and education. Dietitians are involved in research, development of protocols and education.

As with the nurse, it is of concern that the survey of dietitians showed their formal training in IMDs was limited. A few have participated in training rotations at the specialist centres, but most received training and gained experience on the job, which they supplemented as far as they could through personal study and informal contact within the BIMDG specialist group, and training days such as those provided by the BIMDG. Dietetic posts offering training in IMD are very limited. Currently only two specialist centres are known to have rotation training posts for their own staff (London GOSH and Manchester).

An educational opportunity which was highly valued by survey respondents was the current three-day Module 4 of the Advanced Course in Paediatric Dietetics run by the Paediatric Group of the

British Dietetic Association. Module 4 focuses on the practical dietary management of IMD. The Paediatric Dietetics course team is currently working with the University of Plymouth to develop this module further to Master's level, to form part of a Master's degree. This course would have extended content, building on the current Module 4, and would include a total of about two hundred hours' study, with face-to-face teaching and some preparatory and follow-up study in the practitioner's service location. This venture provides an exciting opportunity for further developing and formalising the work of IMD dietitians.

Voluntary organisations

PHGU led a focus group for representatives of voluntary organisations. Following presentation of the background and some of the main preliminary findings, the group was asked to discuss their experiences of services, and their views on the main unmet needs for service users, focusing on diagnosis, initial treatment and long-term care.

A prime concern was for better awareness in order to make a diagnosis for professionals involved in health and other services. Around the time of initial diagnosis, it was important that those in contact had sufficient knowledge to be able to give advice both about immediate care and longer-term needs. It was commented that initial services often did more harm than good because of lack of specialist knowledge and expertise, but were frequently reluctant to refer to more specialised services.

In general, it was thought that fewer than half the patients with IMD were being looked after by specialist services. All should have access within a reasonable distance, but the current experience was of long journeys for many. Emergency services for the many acute crises experienced by patients were often difficult or traumatic, with patients being inadequately managed locally and having to contact specialist services themselves in order to get advice. Networks and formal shared care arrangements between local hospitals and specialist centres would help greatly. In addition, patients and their families were acutely aware of the vulnerability of specialist services; they were often dependent on the interest and energy of one single professional. Voluntary groups were keen that services should be established on a firmer basis. Services for adolescents and young adults were also deficient. As with many chronic diseases, long-term care, respite care and crucial services for those with disabilities such as incontinence services were miserably lacking.

Specialist commissioning in IMD

Specialised services are defined as services with low patient numbers but which need a critical mass of patients to make treatment centres cost effective. Currently, 36 specialised services are designated by the Department of Health. Primary Care Trusts (PCTs) are responsible for commissioning health care services for their populations. However, arrangements exist for specialised services to be commissioned collaboratively by groups of PCTs via specialist commissioning groups. A very small number of services, including LSDs, are commissioned nationally by the National Specialist Commissioning Advisory Group (NSCAG).

At a subnational level, Local Specialised Commissioning Groups (LSCGs) are usually coterminous with Strategic Health Authorities (around 10–15 PCTs) with a planning population of 1 million to 2 million. Specialised Commissioning Groups (SCGs) usually involve 2–5 LSCGs (45–50 PCTs), with a planning population of 3 million to 6 million. Each group has its own commissioning team. All PCTs belong to LSCGs, and all PCTs are represented on SCGs. Strategic Health Authorities are responsible for approving these arrangements and performance management. It should be noted that there is no standardised approach to commissioning in these groups. Each provider and commissioner therefore needs to understand what the local arrangements are. This complexity means that the implementation of national developments and the creation of networks across

organisational boundaries can be challenging and is of great concern with regard to IMDs.

A new survey for this report of specialised services commissioning groups has found that knowledge of IMDs is limited and that mechanisms for commissioning IMD services are unclear and extremely variable. A number of other key issues were identified, including problems managing the transition from paediatric to adult services, cost implications of replacement therapy, workforce planning and training, the limited role of NSCAG, and the development of clinical networks and multi-disciplinary teams.

A number of recommendations to improve commissioning for IMDs are made. These include raising the profile of IMDs, enabling and supporting the commissioning process through education, investigating models of non-NSCAG national commissioning, and providing more information to support commissioning (including a national register).

The future

The future for IMDs will be one of more rather than fewer cases, and greater rather than less complexity and specialisation of care.

Greater awareness and new laboratory techniques – using, for example, tandem mass spectrometry – will identify more cases, perhaps also recognition of milder or different forms of disease that were previously unrecognised, or presentation in adulthood rather than childhood. Molecular and other laboratory techniques that can identify further affected family members will also increase the number of cases diagnosed. In addition, a pilot of newborn screening for MCADD has already led to the identification of new cases. Roll-out of this programme across the country would require increased levels of services to be available to provide expert management for these children.

Further screening tests undertaken by tandem mass spectrometry would exacerbate this. There are also a growing number of new disorders / new areas of metabolism that impact on the need to develop new diagnostic tests and will have implications for monitoring.

The development of new and better treatments – including ERTs, new pharmacological agents, specialised dietary regimes and other treatments such as bone marrow transplantation in mucopolysaccharide and related disorders – has also meant that more children will survive into adulthood. At the same time, this creates a demand on specialised paediatric and adult services to provide continuing management.

Finally, the advocacy of voluntary groups, and increased levels of awareness of patients who seek out information about their condition and how it is best treated, will lead to a situation where they will not accept management from clinicians who lack specialist expertise.

Recommendations

Our Report examined through a detailed look at the structure and process of specialist services, the extent to which these services are likely to be meeting the needs of patients across the country by the provision of high-quality services. Our findings are summarised in Chapter 11. It is thought likely that effectiveness and quality of services is limited by inadequate specialist availability, lack of critical mass for specialist services in most areas, lack of formal recognised education programmes for specialists and a lack of formalised processes for linking services with networks of less specialised providers, and other tertiary specialists such as cardiology or genetics.

Our main recommendations are set out below. Further detail on these is set out in the individual chapters.

1 Strategic overview

Department of Health should commission the British Inherited Metabolic Disease Group in partnership with the National Metabolic Biochemistry Network to establish a formal UK-wide strategic advisory group with links to the Genetics Commissioning Advisory Group and mechanisms for the commissioning of specialised services to maintain an overview and guide strategy implementation for the development of inherited metabolic disease services. The group should include representatives of each service network, commissioners and the voluntary sector. This group should also have responsibility for the development and maintenance of a register of patients and families with these conditions, information on workforce and a database of service provision.

2 Commissioning

The Department of Health in its strategic approach to commissioning specialised services should take specific and explicit notice of the need to commission specialist services for patients with inherited metabolic disease. This will require that the profile of IMD is raised, and might be enabled by commissioning on the basis of three or four supra SCG commissioning groups, possibly each focussing on a regional centre or network of providers.

Commissioning should be for the whole patient journey from newborn screening (where appropriate) through diagnosis to long term clinical management.

The current acute deficiencies in some regions, most notably East Midlands and Southwest must be rectified as a matter of urgency.

The lack of adult services in West Midlands, Southwest and some Scottish services must be addressed as a matter of urgency.

3 Laboratory services

These must continue to be strengthened through the UK National Metabolic Biochemistry Network and continue to maintain close links with molecular genetics services. In particular there are the following needs:

1. Continued provision and further development of specialised laboratory services as an integral part of the multi-disciplinary team for IMD. This requires detailed planning for the preservation and enhancement of laboratory skills to ensure the provision of these specialised services. (This is particularly important for the very rare tests available in only

one or two centres across the UK).
2. Increased workforce resources to enable specialist test provision for the very rare tests, improved turnaround times and more formalised out of hours services.
3. Greater capital investment in expensive specialist equipment and comprehensive replacement programmes.
4. Continuation of investment in higher specialist metabolic biochemistry training for health care scientists beyond the current three year plan from the DH Genetics moneys, and extension across the whole UK.
5. A review of accommodation in the context of the overall plan for IMD services and newborn screening developments across the UK.
6. Development of a formal database in which all laboratory IMD diagnoses are recorded to provide information for service planning, monitoring and audit.
7. Detailed planning for the preservation and enhancement of laboratory skills for the provision of these specialised scientific services.

4 Clinical provision

Specialist providers and specialist commissioners must discuss and agree overall configurations of services so that centres and/or networks are able to provide services to an agreed regional population and covering the entire UK between them. This should include newborn screening, specialist laboratory services and the clinical multi-disciplinary team.

The absence (East Midlands) and extreme deficiency (Southwest) of services in some regions must be addressed as a matter of urgency.

The lack of adult services in West Midlands, Southwest and some Scottish services must be addressed as a matter of urgency.

Initially providers should come together on a regional or supra-regional basis to ensure that they can provide the following for their populations and, where services do not meet these requirements, to publish a detailed action plan:

1. Coordinated and integrated paediatric, adult and laboratory services.
2. Services appropriate to handle the IMD workload arising from newborn screening.
3. A critical mass of professionals as multi-disciplinary team to provide 24-hour care and to ensure robustness and continuity of services. This should include laboratory, medical, nursing and dietetic professionals immediately, with expansion to include pharmacy and psychologists when possible.
4. Formal arrangements with supporting tertiary specialties to provide wider specialist expertise.
5. Arrangements for tertiary services to support district general hospitals.
6. Education and training for all groups of specialist professionals, those providing specialist care in other specialties, and, as appropriate for secondary and primary care providers.
7. Clinical and laboratory databases to monitor and audit.
8. Supporting information to commissioners.

Commissioners and providers will need to plan for an expansion of clinical services and resources to approximately double across the UK to cope with current unmet needs. This should be kept under review in the light of:

- trends in numbers of new cases reported by the specialist laboratories (a database will be required for this)
- findings of the pilot studies on extended newborn screening and policies of the National

Screening Committee to extend this further
- expert guidance based on knowledge and understanding of the availability and outcomes of new tests and treatments

5 Education

Workforce planning, training and education should take place on a national basis because inherited metabolic disease is a small speciality, and there will only be a handful of centres able to provide the full range of educational opportunities.

Working groups should be set up to plan education for laboratory scientists, medical, dietitian and nursing professionals advised by the National Workforce Review Team and others as appropriate.

The current plans to develop Module 4 of the Advanced Course in Paediatric Dietetics (focussing on management of inherited metabolic disease) to Master's Level as part of a Master's degree should be supported.

Developments for specialist nurses at Master's level are also recommended.

The laboratory clinical scientists are key members of the team and, there is a cohort of trainees in training with lead trainers in England. However, there is a need to plan beyond this single intake. There is also a need for vocational MSc training for biomedical scientists.

Finally, the professionals themselves should work together and be provided with time and resources to develop educational material for use with other professionals and patients.

6 Audit

The disparity between the numbers of patients in contact with service and likely total numbers illustrates the need to be able to keep in contact with patients, both to enhance their individual care and for service planning, audit, and eventually also research.

There should be a national register of patients with IMD using consistent definitions and diagnostic criteria wherever possible.

The register should be linked to laboratories providing diagnostic services, the national screening programmes for IMDs and voluntary and commercial groups representing the interests of patients with certain disorders.

7 Voluntary organisations

Clinical networks should work closely with and support voluntary agencies to provide information about specialist services to professionals, members, patients with IMD and the public.

Voluntary organisations should be supported and encouraged to be involved in the provision of educational material and programmes on IMDs for professionals.

8 Resources

The estimates for resource requirements (Table 5) are based on a total of seven networks across the UK and assume an approximate doubling of the workforce (necessary as soon as possible to meet unmet need noted as estimated numbers of patients not in contact with specialist services).

The main areas for increased resources requirements are:

- To develop infrastructure
- To increase clinical workforce
- To ensure adequate laboratory provision
- To develop education and training programmes

It should be noted that this table simply represents a possible **order of magnitude** for investment that should be made in the services over the next 3-5 years. The ability to develop services in this way depends on being able to recruit and train the extra staff, should funds and new posts become available. Costings do not include the cost of developing Master's Courses for nurses and dietitians, nor of sending individuals on these courses. Such estimates would require more detailed work. Estimates also do not include costs of developing and maintaining a national register. Some of this would be met by the development of the database, but final costs would depend on the nature and purpose of the register and would need to be the subject of a separate proposal. Finally, costs represent salaries and associated costs, but not the costs of the extra clinical work undertaken by these individuals (eg out-patient, drug costs etc). In general, the estimates should be considered as a **minimum**.

It can be seen that the total extra annual investment over the entire UK is approximately £7 million, or about £1 million per network.

Table 1.5 Estimate of minimum development costs for IMD services

Infrastructure	Annual expenditure £ thousands	Basis of calculation
Strategic Advisory Group (12 people) (7 network representatives, 1 voluntary organisation, 1 commissioner, representatives of BIMDG and Metbionet) educational lead		
Meetings	2.5	For 12 persons for 4 meetings per year
Administration	2	Administrative secretary (0.1WTE)
Database managers for the 7 networks (6 X 0.5wte and 1 X 1wte for coordination)	126.5	Salary calculated for 4 database managers SNP 26)
Website development and maintenance	6.5	Charges for maintaining the website (domain and hosting) = 200 Salary for a webmaster calculated at 0.2 WTE (SMP 26) 6,300
		To increase clinical provision
Medical consultant 24 new posts (WTE)	3000	Calculated at 520 sessions per year for each consultant
Nursing posts 24 new posts	900	Based on WTE salary for grade G for 24 posts
Dietitian posts 24 new posts (approx 1 consultant per network, 3 specialists or senior dietitians per network)	875	Calculated on basis of 7 consultant, 9 specialist and 8 senior dietitians (dietetic assistants not included)
Psychologists (0.5 per network) (Some networks already have)	105	Assumed grade 'A' for the posts

Laboratory provision		
Specialist capital equipment*		
Urgent replacement of amino acid analysers**	300** non-recurrent	
Annual replacement costs	600	
Education and training		
Trainers (clinical)		
Part time trainer for each network	91	Calculated at 1 session (4 hours) for 7 networks
Funding for the new training posts	308	Calculated at WTE for a SpR
Training (laboratory)		
Trainers (3.0 across UK)***	245	Current costs
Clinical scientist trainees (10 wte across UK)	354	Current costs
Biomedical scientists (9 across UK)	320	Current costs
TOTAL	**6935.5**	

* this is equipment that would not be part of a general biochemistry department (ie amino acid analysers, GCNS and tandem mass spectrometers)
** one-off cost
*** Required from 2007/08 DH Genetics funded until then

Notes:
All salaries based on mid-point of the scale.
Workstation costs (excluding capital expenditure) will amount to £1,000 per person.
Set-up costs (computer and other equipment) could amount to £1,500 per person.
Travel, staff development and other expenses are not included.

Conclusion

In conclusion, we acknowledge the commitment of individuals and teams of professionals in providing excellent services to their patients with inherited metabolic disease as far as they are able. However, the lack of planning, resourcing and commissioning to provide comprehensive services to the entire population has meant that many patients do not have access to these services. Those that do must frequently find the services overstretched, limited in scope and unable to offer care tailored to their individual needs – including, for example, shared care arrangements which allow them to be looked after near home under the guidance and supervision of experts when necessary.

Parents of children and patients themselves, have some of the biggest challenges of severe and chronic disease. Parents learn to provide complex treatment regimes; they recognise and deal with the acute crises, that can occur at any time; they have to deal with a lot of other specialists, as their child has complications and problems with various organ systems; they may need to understand and take difficult decisions over the familial aspects of the condition. On top of all this, their energies may be almost totally consumed by coping with a child with a severe disability, and all that this entails in terms of everyday life, education and work opportunities.

We believe that the evidence is now available on which services suitable for this patient group could be developed in the UK by fairly modest investment and some reorganisation. Taking this opportunity now would enable the NHS to cope with likely increased demand arising from expanded screening services and new treatments and provide a service that more nearly meets the needs of this population.

References

i British Inherited Metabolic Disease Group. *Inherited Metabolic Disorders: A Service Vision and Standards of Care 2004*.

ii Dionisi-Vici et al. Inborn errors of metabolism in the Italian paediatric population: a national retrospective study. *J Pediatr* 2002:140:321–7

Section Two Evidence

2 Epidemiology

1 Introduction

Currently, there are well over five hundred known IMDs. This number is increasing as our knowledge of human metabolism advances and our ability to detect problems develops. Whilst each individual disorder is usually rare, the collective cumulative incidence is substantial: estimates of 1 in 2,500–5,000 live births are commonly quoted, although it is difficult to identify the primary sources for these figures. Increasing numbers of patients are surviving into adolescence and adulthood as a result of earlier detection (e.g. through expanded neonatal screening programmes) and improved treatment (including specific replacement therapies, such as *Cerezyme* for Gaucher disease).

2 Definitions

IMDs are classically defined as *monogenic diseases resulting from deficient activity in a single enzyme in a pathway of intermediary metabolism*. Clinical consequences arise from the accumulation of substances usually present in small amounts, deficiency of critical intermediate products or specific final products, or the toxic effects of products derived from alternative metabolic pathways.

This definition includes disorders in the catabolic and synthetic pathways of carbohydrates, amino acids, the urea cycle, and organic and fatty acids; as well as purines and pyrimidines, porphyrins, steroids, lipids and bile acids. Also included are disorders of lysosomal enzymes and pathways involving trace metals (such as copper) and essential co-factors (such as molybdenum). The definition excludes other inherited disorders of connective tissues, blood and blood-forming organs (such as haemophilia), immune system, muscle (but not those resulting from intermediary metabolism problems, such as certain glycogen storage diseases) and skin.

3 Classification systems

A number of classification systems for IMDs exist. One of the most widely used is that of Saudubray and Charpentier, which classifies disorders according to the clinical phenotype. Other systems base their classification on the primary compound (e.g. carbohydrates or amino acids), size of molecule involved, or whether the disorder affects specific organelles or not (such as LSDs). This means that glycogen storage diseases can be classified as *carbohydrate* disorders (ICD10), *small molecule* disorders (Applegarth), or *energy deficiency* disorders (Saudubray). Certain disorders can be classified in more than one category; for example, Pompe disease can be justifiably defined as a glycogen storage and as an LSD, and cystinosis can be categorised as an amino acid disorder and as an LSD.

Because of the very large number of IMDs, Appendix 2.1 in this chapter lists examples of some of them by the main categories. Of these disorders, the majority present within childhood and, for many, few patients survive into adulthood – although the number of survivors is increasing with new treatments. The survivors include Gaucher disease type I, and amino acid disorders such as phenylketonuria (PKU). A number of IMDs only present in adulthood; these include certain glycogen storage diseases, Wilson disease, certain porphyrias and familial hypercholesterolaemia. There are also a number of other important considerations about IMDs as a whole:

- They are genetic disorders, so their detection has implications both for the person diagnosed and their family.
- Certain disorders are closely linked to ethnic origin (e.g. Ashkenazic Jews and Tay-Sachs

disease, Wilson disease in Sardinian Italians). These differences have also been observed in ethnic groups in the UK.
- Their clinical consequences are often severe, with high mortality and morbidity, requiring intensive long-term intervention, factors compounded by their rarity; they are generally low-volume, high-cost conditions.
- Early detection via newborn screening and treatment can make significant improvements on the outlook for a number of conditions (e.g. PKU and certain LSDs).

4 Estimates of disease incidence and prevalence from published literature

4.1 Incidence

Table 2.6 (Appendix 2.2) shows incidence (birth prevalence) figures derived from a number of sources in the published medical literature and attempts to estimate the annual number of new cases in the UK. Table 2.1 ranks these conditions by their estimated annual incidence in the UK. The "birth prevalence" is widely used as a proxy for a true incidence rate throughout the literature on IMDs. This is because it is difficult to define the true population at risk (all embryos) and a quasi-population at risk (live births) is used instead. In this context, the birth prevalence can be regarded as an *incidence proportion* (also known as cumulative incidence), assuming that the rate of post-natal diagnosis is equal to the birth rate for each disorder (complete ascertainment). Whilst this assumption has its problems, it is consistent with the approach adopted in similar, published studies. The methods described by Dionisi-Vici and Meikle have been used for all calculations to ensure comparability with other similar, published studies. Despite its limitations, the birth prevalence provides a useful proxy for incidence that is of practical use.

Table 2.1 Disorders ranked by their estimated annual incidence

Disorder	Number of new cases per year
Familial hypercholesterolaemia	1442
Organic acid disorders	264
Acute intermittent porphyria	150
Fatty acid oxidation disorders	132
LSDs	111
Amino acid disorders	105
Peroxisomal disorders	27
Urea cycle disorders	26
Wilson disease	26
Mitochondrial disorders	25
Carbohydrate metabolism (glycogen storage disorders)	23
Carbohydrate metabolism (other disorders)	18
Miscellaneous	180
Subtotal (excluding familial hypercholesterolaemia)	1087
Total	**2529**

Familial hypercholesterolaemia (FH) has the highest incidence. This condition tends to be diagnosed much later than most of the 'classic' IMDs, and is usually dealt with by lipid clinics rather than IMD centres. However, these figures are only part of the picture because overall survival and survival to reproductive age are important factors in determining the prevalence of each disorder, and so the burden of disease in the population.

It is interesting to compare the projected incidence with actual incidence, but difficult to draw strong conclusions because the discrepancy may be due to deaths being attributed to other causes, to presentations where a definitive diagnosis has not been made, or to mild cases being undetected; as well as to important problems with the data, classification schemes and applying international estimates to the UK.

We have also used another approach to estimate incidence, using data from diagnostic test results from the five most recent complete years (1999–2003) from the West Midlands Regional IMD Laboratory (Table 2.2). The region has a total population of 5.2 million and its boundaries have remained unaltered by NHS reorganisations. Approximately 15 per cent of the population are from black and ethnic minority groups. For some disorders – such as metals, lipids and steroids and porphyrin and haem – this will provide an underestimate as some cases will have been diagnosed by other laboratories.

Table 2.2 Incidence of IMDs in the West Midlands, based on number of new diagnostic test results

Condition	Five-year average number of cases	Birth prevalence per 10,000 live births	Number needed to diagnose one case	*Upper 95% ci*	*Lower 95% ci*
PKU	5.00	0.81	12420	5008	33784
Other amino acid	11.60	1.87	5354	2943	9990
Urea cycle defects	2.80	0.45	22179	6702	90909
Carbohydrate	3.80	0.61	16343	4509	52910
Organic acid	7.80	1.26	7962	3837	17301
Glycogen storage	4.20	0.68	14786	5504	44643
Lysosomal storage	12.00	1.93	5175	2874	9551
Purine and pyrimidine†	0.80	0.13	77628	12063	2000000
Fatty acid oxidation	4.80	0.77	12938	5123	35971
Peroxisomal	4.60	0.74	13500	5244	38462
Mitochondrial	12.60	2.03	4929	2776	8953
Metals‡	2.20	0.35	28228	7418	147059
Lipids and steroids#	4.00	0.64	15526	5647	48544
Porphyrin and haem*	1.00	0.03	310510	10070	3333333
Miscellaneous	2.80	0.45	22179	6702	90909
Total	**79.20**	**12.8**	**784**	**619**	**970**

These figures suggest that the often-quoted figure of 1 in 2,500 live births for the incidence of IMDs is a substantial underestimate of the likely disease burden, especially in ethnically diverse UK populations. These data are consistent with other published studies (see Dionisi-Vici) and they should prove to be very useful in the planning and provision of IMD services.

Two other important issues are the impact of ethnicity and consanguinity on the incidence of metabolic disorders. Ethnicity acts as a 'marker' for assessing the ancestral genetic history of populations. Certain ethnic groups have higher incidences of certain disorders, which can arise from founder effects, selection effects, genetic drift and migration and consanguinity. Ethnic groupings may also have 'hot spots' where certain IMDs may be especially common, relative to the overall national average incidence.

Consanguinity specifically increases the risk of recessive disorders, whilst membership of an ethnic group may impact upon disorders with different modes of inheritance. In a study of IMDs in the

West Midlands, Hutchesson and colleagues found that the overall frequency of IMDs was ten times higher in Pakistani children than white children (1 in 318 v. 1 in 3,760). This particular ethnic group has a cultural preference for consanguineous marriage, which may well account for the increase in the incidence of IMDs. Other groups with a similar preference include some Bangladeshis, Indian Muslims and residents of Middle Eastern origin. However, consanguineous marriage also occurs within the white majority population, with up to one third of all marriages being consanguineous.

4.2 *Age at diagnosis and survival: moving towards prevalence estimates*

There are very few published data on the prevalence of IMDs as a group, although there are studies for a few specific disorders. The study by Dionisi-Vici in Italy has provided some data on the median age at diagnosis for IMDs and the proportion of patients surviving into adulthood. Table 2.3 shows the median age at diagnosis for different classes of disorders.

Table 2.3 Median age at diagnosis for IMDs

Disorder class	Median age at diagnosis
Small molecules (organic acidopathies, urea cycle, amino acidopathies,fatty acid oxidation)	9 months
Sugars	1.5 years
LSDs	3 years
Peroxisomal	8 years
Mitochondrial	2 years
Others	5 years

This study found that 11 per cent of people with IMDs were surviving past the age of 18 years. This was considered to be a minimum estimate because of the effect of earlier age of diagnosis for most conditions and a short follow-up period for their study. It also did not include conditions such as FH and acute intermittent porphyria, which are often diagnosed in adulthood or beyond.

The commonest disorders in these survivors were Gaucher disease 1a and amino acid disorders (especially PKU). Mortality was highest in the primary lactic acidaemias, other LSDs and peroxisomal disorders. Nevertheless, these figures show that the greatest burden of disease remains in the paediatric population. Survival is highly variable, depending on the disorder studied and the potential impact of interventions.

A combination of the discovery of new disorders, better clinical recognition of known disorders and improved clinical management means that, over time, the prevalence of IMDs is increasing, as is the number of patients surviving into adulthood. The main burden of disease is in infants and in late childhood, but this is now being extended to older age groups.

4.3 *Mortality from IMDs*

The three most recent years of ONS mortality statistics data were analysed by primary cause of death (Table 2.4). Previous years were not analysed because of the changeover from ICD9 to ICD10 and subsequent interpretational difficulties. There will also be a number of death certificates that may cite IMDs as an underlying cause of death; these are not captured easily from official statistics, IMDs are often not consistently reported on death certificates, and a specific IMD may not even have been considered by the certifying doctor.

Although the absolute number of deaths is relatively small, the main burden is in those under the age of 14 years (around 75 deaths a year, with around 30 a year in those aged under 1 year) and

over the age of 35 (around 120 deaths a year). The last-mentioned deaths are almost exclusively caused by lipid disorders; if these are removed from the total, virtually all of the burden of mortality is in those aged 14 and under.

The commonest causes of death in those aged under 1 year were urea cycle disorders, glycogen storage diseases and congenital malformation syndromes (which include peroxisomal disorders such as Zellweger); in those aged 1–4 years, GM2 gangliosidosis and sphingolipidosis; in those aged 5–9 years, sphingolipidosis; and in those aged 10–14 years, also sphingolipidosis.

Table 2.4 Mortality from IMDs 2001–2003 as primary cause of death by year of death and by cause

	2001	2002	2003	Cause
	Number (% total)	*Number (% total)*	*Number (% total)*	
<1	34 (15.8)	24 (11)	24 (12.4)	Urea cycle GSD
1–4	20 (9.3)	29 (13.3)	22 (11.3)	GM2 GS Other SL
5–9	11 (5.1)	9 (4.1)	9 (4.6)	Other SL
10-14	14 (6.5)	13 (5.9)	10 (5.1)	Other SL Other MPS
Subtotal	**79 (36.9)**	**75 (34.4)**	**65 (33.5)**	
15–34	10 (4.7)	11 (5)	18 (9.3)	
35–54	29 (13.6)	23 (10.6)	20 (10.3)	Lipidaemias
5569	43 (20)	31 (14.2)	30 (15.5)	Lipidaemias
70 and above	53 (24.8)	81 (37.1)	61 (31.4)	Lipidaemias
Total	**214**	**218**	**194**	

Not a complete year's data.
GSD = glycogen storage disease
MPS = mucopolysaccharidosis
SL = sphingolipidosis

4.4 Interpretation problems

Interpreting the epidemiological data on IMD is fraught with problems. This section briefly describes some of the key issues.

The nature of the disorders themselves

- **Rarity.** Most IMDs are exceedingly rare, resulting in very small numbers of cases, even in large populations. These low numbers mean that random variation in the incidence is high, and incidence rates and prevalence proportions will have very wide confidence intervals.
- **Clinical heterogeneity.** Many conditions demonstrate high levels of phenotypic variability. This can lead to mistaken diagnosis if there are overlaps with other clinical conditions that present in similar ways.
- **New disorders being discovered.**

Primary data problems and changes in diagnosis

It is highly likely that the true incidence of IMDs is relatively constant in populations as most are caused by single-gene disorders; the variant-gene frequencies are likely to remain stable in large, out-breeding populations over the time scales we are interested in. Reported increases in incidence

are therefore more likely to be artefacts arising as a result of the following:

- Changing diagnostic criteria and coding; for example, changes in the International Classification of Diseases from version 9 to 10 which came into effect during 2000 and 2001.
- Changing detection technologies or strategies; for example, introducing neonatal screening programmes and/or the use of new techniques such as tandem mass spectrometry in diagnosis and screening.
- Different diagnostic criteria and detection methods within and between populations.
- Both increased recognition and underdiagnosis.
- Data sources: the incidence of IMDs is much 'higher' in areas where neonatal screening programmes for specific disorders exist. A study in Italy found that incidence rates for galactosaemia were 12 times higher in regions with neonatal screening programmes. However, this is not the case for galactosaemia in the UK.
- Changes in all these factors over time: because of the rarity of IMDs, many studies investigating incidence use long-time series; as a result, they are even more vulnerable to these kinds of problems.

The prevalence of IMDs is increasing because of some of these factors, as well as improved treatment and survival; this has implications for the provision and planning of appropriate clinical services for patients with IMDs.

One of the major problems is that UK-specific data are very limited. Given the large international variations in incidence, it is difficult to know how applicable their results are to the UK.

Genetic factors

As IMDs are generally single-gene disorders, underlying genetic factors can influence their epidemiology:

- **Genetic heterogeneity.** This is divided into two types. Locus heterogeneity occurs when genetic variants at different loci can cause the same disorder. Allelic heterogeneity occurs when different genetic variants at the same locus can cause the same disorder. Therefore, diagnostic or screening strategies and epidemiological studies based on the underlying genetics of IMDs can come to different conclusions in different populations.
- **Population history.** The history of specific populations, with expansion and bottle-necks, can influence the presence of these disorders in certain populations.
- **Founder effects.** Certain IMDs are especially common in certain populations (e.g. in Ashkenazic Jews). These populations are derived from a small number of ancestors who carried the variant genes.
- **Heterozygote advantage.** This is postulated as an important factor, explaining why some of these apparently harmful genes survive in human populations and are not removed through natural selection.
- **Penetrance and expressivity.** Both of these factors apply especially to autosomal dominant conditions. Certain conditions have a high penetrance, so that most of those possessing the harmful gene express the disorder. The opposite is true for low penetrance conditions. Expressivity refers to the extent of the disorder in the phenotype: some people may have very severe disease whilst others have very mild disease. This can affect the ability to diagnose certain conditions accurately.

5 Outcome studies

These studies are greatly hampered by the small numbers of people suffering with IMDs. In many cases, the only evidence on outcome survival is derived from small case series. Assessing the effectiveness of treatment or other interventions may also be affected (quite rightly) by ethical considerations, particularly whether randomisation to placebo can be justified. The problems of outcome studies are considered in more detail elsewhere in the report.

In general, the outcome for most IMDs is poor, with increased mortality in childhood and early adulthood and with severe symptoms – including neuro-degenerative disorders, metabolic abnormalities, multi-system pathology, and others specific to each disorder.

6 Recommendations for the future

Research in this area and service planning would be greatly helped by establishing national and international registers of IMDs, using consistent definitions and diagnostic criteria wherever possible, and collecting data on ethnicity and consanguinity. Other rare conditions have benefited from this kind of arrangement (e.g. the national UK bone malignancy register) as they provide a resource for research, service planning and organisation. A register could be linked to the laboratories providing diagnostic services as well as to voluntary or commercial groups representing the interests of patients with certain disorders. Developments in national screening for IMDs, which are currently being evaluated by the NHS Health Technology Assessment programme and the National Institute for Clinical Excellence (NICE), could also help establish useful data. A register would allow prevalence to be estimated, which would be extremely useful for service planning, given the lack of current information on this subject.

Summary

1. There are well over five hundred known IMDs.
2. There are a number of different ways of classifying IMDs, which can lead to some confusion.
3. Although they are rare, collectively they are common: an incidence (strictly birth prevalence) of 1 in 2,500–5,000 live births is often quoted.
4. Whilst there are some international data, there are few that are specific to the UK.
5. Data from the West Midlands suggest that the incidence of IMDs in a UK population is 1 in 784 live births, substantially higher than the 1 in 2,500–5,000 estimate.
6. Although there are data on the birth prevalence of these conditions, there are virtually no data about adult or childhood prevalence and survival, except for a few, highly selected conditions.
7. We have estimated that there are probably around a thousand incident cases per year of the core disorders in the UK.
8. Ethnicity and consanguinity are key factors for determining the incidence of certain disorders in populations.
9. Around two hundred people die each year from IMDs as a primary cause of death. About 40 per cent of these deaths occur in those aged 14 and under.
10. The data available need to be interpreted carefully as there are a large number of problems in ascertaining, classifying and coding IMDs, especially for those with variable clinical presentations.
11. A national register of patients with IMDs would be a great help for those studying IMDs and those planning, procuring and monitoring services.

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Appendix 2.1

Table 2.5 Sample IMDs by the main categories

Category	Condition
Amino acid disorders	PKU Homocystinuria Maple Syrup Urine disease Tyrosinaemia
Urea cycle disorders	Carbamyl synthetase deficiency Ornithine carbamyl transferase deficiency Citrullinaemia Arginosuccinic aciduria
Carbohydrate disorders	Galactosaemia Fructose disorders
Organic acid disorders	Isovalearic acidaemia Methymalonic acidaemia Glutaric acidaemia type I Methylglutaric acidaemia Propionic acidaemia Biotinidase deficiency
Glycogen storage disorders	Glycogenosis I (Pompe) Von Gierke Cori Andersen McArdle
LSDs	Mucopolysaccharidoses Pompe Hurler Hunter Morquio
Sphingolipidoses	Gaucher Anderson-Fabry Tay-Sachs Niemann-Pick
Purine/pyrimidine disorders	Hereditary xanthinuria Lesch-Hyhan Adenosine deaminase deficiency Adenylate deaminase deficiency
Fatty acid oxidation defects	MCADD LCAD SCAD
Peroxisomal disorders	Refsum Zellweger Adrenoleukodystrophy
Mitochondrial disorders	Oxidative phosphorylation disorders Pyruvate disorders
Trace metal disorders	Wilson Menke Molybdenum co-factor deficiency
Glycoproteinoses	Fucosidosis Mannosidosis Associated conditions
Lipid and steroid disorders	Familial hypercholesterolaemia Congenital adrenal hyperplasia
Porphyrin and haem disorders	Hepatic porphyrias Erythropoietic porphyrias

Appendix 2.2

Table 2.6 Incidence of IMDs: international estimates, UK estimates and predicted numbers of new cases per year

Category	Condition	International incidence (live births)	UK incidence (live births unless specified otherwise)	UK number of new cases a year (denominator UK 793,000 live births; UK data used if possible)
Amino acid disorders	PKU		1 in 12,000	66
	Homocystinuria	1 in 291,000	1 in 234,000	3
	Maple Syrup Urine disease	1 in 185,000	0 in 494,000	0?
	Tyrosinaemia		1 in 105,000	7
	Total all amino acid		*1 in 7,500*	*105*
Urea cycle disorders	Carbamyl synthetase deficiency			
	Ornithine carbamyl transferase deficiency	Wide international variation 1 in 70,000 Italy		11
	Citrullinaemia	1 in 500,000 Canada		1.6
	Arginosuccinic aciduria	1 in 80,000–500,000		1.6–10
	Total all urea cycle	*1 in 30,000*		*26*
Carbohydrate disorders				
Non-glycogen storage	Galactosaemia	1 in 26,000–669,000	1 in 44,000	18
	Fructose disorders	1 in 147,575 Italy		5
Glycogen storage	von Gierke	2 per 100,000		16
	Pompe			
	Cori			
	Andersen			
	McArdle			
	Total all glycogen storage	*1 in 34,000 Italy* *1 in 43,200 Canada*		*23* *18*
Organic acid disorders	Isovalearic acidaemia			
	Methymalonic acidaemia	1 in 61,775 Italy	13	
	Glutaric acidaemia type I			
	Methylglutaric acidaemia			
	Propionic acidaemia	1 in 166,302 Italy	5	
	Total all organic acids	*1 in 3,000 (common) – 15,000 (rare)*		*53–264*
	Biotinidase deficiency	1 in 112,000 (profound) 1 in 129,000 (partial)		7 6

Category	Condition	International incidence (live births)	UK incidence (live births unless specified otherwise)	UK number of new cases a year (numbers based on UK incidence rates in bold)
LSDs				
Mucopolysaccharidoses	Pompe	2 per 100,000		16
	Hurler	1.2 per 100,000		10
	Hunter	0.67 per 100,000		5
	Morquio	0.21 per 100,000		2
Sphingolipidoses	Gaucher	2 per 100,000, NL		16
		1 in 40,000, Italy		20
	Anderson-Fabry	1 per 100,000		8
	Tay-Sachs	0.41 per 100,000		3
	Niemann-Pick	0.35 per 100,000		3
	Total all lysosomal storage	*14 per 100,000 NL*		*111*
		1 in 8,275 Italy		*95*
Purine/pyrimidine disorders	Hereditary xanthinuria	1 in 70,000		11
	Lesch-Nyhan	1 in 380,000		2
	Adenosine deaminase deficiency	1 in 380,000		2
	Adenylate deaminase deficiency†	1 in 150		5,287
Fatty acid oxidation defects	MCAD	1 in 9,000 USA	1 in 6,000–20,000	40–132
	MCADD			
	LCAD			
	SCAD			
	Total all fatty acid oxidation	*1 in 91,600 Italy*		*9*
Peroxisomal disorders	Refsum			
	Zellweger			
	Adrenoleukodystrophy	1 in 82,800 Italy		10
	Total peroxisomal	*1 in 29,000 Canada*		*27*
		1 in 71,800 Italy		*11*
Mitochondrial disorders	Oxidative phosphorylation disorders			
	Pyruvate disorders			
	Total mitochondrial	*1 in 31,400 Canada*		*25*

Category	Condition	International incidence (live births)	UK incidence (live births unless specified otherwise)	UK number of new cases a year (denominator UK 793,000 live births; UK incidence rate where possible)
Trace metal disorders	Wilson	1 in 50,000–100,000	1 in 30,000–60,000	13–26
	Menke	1 in 250,000		3
	Molybdenum co-factor deficiency	Extremely rare		
	Glycoproteinoses Fucosidosis			
	Mannosidosis			
	Associated conditions			
Lipid and steroid disorders	Familial hypercholesterolaemia (heterozygotes)	1 in 500 average Wide variation in founder populations; as low as 1 in 70 in Afrikaaners	1 in 550–750 total population	1,442
	Congenital adrenal hyperplasia	1 in 10,000–14,000	1 in 12,000 Wales 1 in 21,000 England 1 in 17,100 Scotland	66 38 46
Porphyrin and haem disorders	Hepatic porphyrias (acute intermittent porphyria)	Unknown	1.5 per 100,000 total population	825
	Erythropoeitic porphyrias	Extremely rare		
	Total disorders (excluding FH and AIP)			***937***
	Total disorders (excluding FH)		1,762	
	Total disorders		***7,049***	

3 Effectiveness and quality

Like care for other, more common chronic diseases, our specialist IMD care is directed at achieving a range of improved outcomes for patients and their families. Some outcomes – such as mortality – are more measurable than others, which relate to quality of life; but all are important. As the diseases are varied, the precise nature of the outcomes to be achieved will vary. In some cases outcomes have been investigated and audited for certain diseases and treatments (e.g. control of PKU during pregnancy and pregnancy outcome). However, we found no examples in the UK or worldwide where outcomes for specialist services directed at the whole range of IMDs have been described or investigated.

We set out below the important outcomes for specialist IMD services, which the stakeholder group discussed at various stages. These are illustrated with clinical examples derived from case histories. The aspects of the specialist management that facilitated these outcomes were also described – giving the possibility of setting some standards of structure or process that would be expected to lead to better outcomes.

The main categories of outcome are as follows:

- Decrease in mortality
- Decrease in morbidity
- Reduction in disability
- Prevention of harm to family members
- Prevention of damage to unborn child
- Reproductive choice
- Overall quality of life (reduction of handicap).

Decrease in mortality

A decrease in mortality can be measured as longer survival, older age at death, and a higher proportion of patients surviving into adulthood. Some data on mortality are given in the epidemiology chapter (Chapter 2), where it is reported that about 11 per cent of patients with IMD survive into adulthood. It is expected that more will survive into adulthood as a result of better recognition, improved management and new therapies.

Our case histories illustrate how mortality may be prevented through the following means:

- Better and more rapid initial diagnosis. For example, the child with Maple Syrup Urine Disease (MSUD) in the dietitians' case history (a) (Chapter 8) was encephalopathic and required ventilation and dialysis when transferred from the local DHG to the specialist unit where he was diagnosed and started on emergency dietary management.
- Management of acute crises. The same child required an emergency regime to prevent potentially fatal metabolic decompensation *every time* he developed intercurrent illness.
- Prevention of potentially fatal complications. In case history 4 (Appendix 3), specialists needed to recognise and manage the potentially fatal consequences of childbirth in a woman who appeared to be mildly affected by ornithine carbamyl transferase deficiency.

Decreased morbidity

This includes reduction in number and severity of complications arising from the disease and reduction in disability.

IMDs cause harm to many organ systems, both through deficiency of critical intermediate products or specific final products, the accumulation of products usually present in small quantities 'upstream' of the defect, or sometimes the toxic effects of products derived from alternative metabolic pathways.

PKU is a good example of a condition where harm is caused to various organs by the build-up of intermediate metabolites. Phenylalanine accumulates in the body owing to deficiency in the enzyme that breaks down this substance. High levels cause damage to the nervous system, with severe learning disability and neurological problems. If identified in the newborn, special diets can be instituted which prevent these problems.

Case history 1 (Appendix 3) gives an example of a child with methylmalonic acidaemia (MMA), an organic acid disorder which can present with non-specific symptoms in the newborn. The local paediatrician needed to be aware of the possibility of an IMD, to have access to discuss the case with IMD specialists, and to arrange specialist investigations with the specialist biochemistry service. In this case some neurological damage occurred as the child had brain damage before the diagnosis was made.

Reduction of complications is another issue. The nursing case history (b) (Chapter 7) illustrates how a diagnosis of Fabry disease may lead to ERT, which may slow down the development of renal complications, heart and brain damage.

Reduction of disability

Case history 1 (Appendix 3) shows how, for a boy with MMA, a large number of services needed to be coordinated in order to help deal with the child's disabilities and help his family to cope. Multi-agency support had to be provided in the community, including nursing (to manage gastrostomy and overnight pump feed), physiotherapy, occupational therapy, wheelchair services (for movement disorder and kyphoscoliosis), education and psychology. Coordination of a wide range of services must take place, the specialist team being able to optimise long-term medical care, predict and prevent complications as far as possible, and provide expert advice to the multi-agency team and family.

Prevention of harm to family members

Because these diseases are genetic in origin, other family members may be at risk of the same condition. They may be unaware of this as some have non-specific symptoms, or they may be only mildly affected, or onset might be in later life. However, for some conditions, such as Fabry disease, treatment can be offered with the chance of reducing longer-term organ damage.

In case history (e) (Chapter 7), specialist nurses described the case of a 43-year-old man diagnosed with Fabry disease following the finding of protein in his urine and subsequent discovery of renal damage and cardiac involvement. Three asymptomatic sisters required counselling and screening and two were found to be carriers, with potential risk to any offspring. With knowledge of the family history, a nephew who had presented with a stroke at age 41 was also found to have the disease and his family was also counselled.

Prevention of damage to unborn child

High levels of intermediate metabolites, such as may occur in PKU, cause damage to the unborn child, so it is important that women with IMD are warned of the risk of this and encouraged to seek advice before and during pregnancy.

Dietitians reported the case of a 30-year-old woman with PKU who was treated from birth with

diet (case history (b), Chapter 8). Her diet was relaxed during teenage years, but services had impressed on her the need to go back on a strict diet and ensure good control before and during any pregnancy to ensure that the unborn child was not harmed by the high phenylalanine levels. She attended a period of re-education prior to pregnancy, embarked on her new diet, and was monitored closely during pregnancy, with a successful outcome.

Reproductive choice

Again, because of the genetic nature of the conditions, there may be a risk that the offspring of a patient will also have the disease. Patients need to be counselled about this risk, and advised on their various options to have as healthy a child as possible.

Case history 4 (Appendix 3) presents the case of a woman with OCT deficiency. Although relatively mild in females, this can have very severe and fatal consequences in male offspring. This case shows how a woman was given information about this as a teenager, and was subsequently counselled and supported through a pregnancy, in which she chose to have prenatal diagnosis and eventually a termination owing to the finding of an affected male fetus.

Quality of life

Patients and their families seek to have as normal a life as possible, and not to be limited by disease in their fulfilment of educational and social potential. They want to achieve the maximum in educational attainment, having a job, integrating into society, participating in family life and generally experiencing psychological well-being.

The role that specialist services may play is described in the nursing case history (d) (Chapter 7). The specialist nurse looking after a teenage girl undergoing treatment for Fabry disease described multi-disciplinary work in caring for the 17-year-old, who became depressed and exhibited self-harming behaviours, including self-abuse with alcohol, drugs and sexual promiscuity. The nurse was instrumental in obtaining and coordinating support from the mental health crisis team, from counselling, and from drugs and alcohol rehabilitation teams in statutory and voluntary agencies.

The role of voluntary organisations is extremely important in helping families adapt and cope with an IMD and get the most out of life. Voluntary organisations can usually give personal support, advice and guidance to parents at the time of diagnosis; provide information about the condition; put parents in contact with other families affected by the condition; and help them to cope with complex therapies or difficult behaviours. Very importantly, they often also act as advocates for the family to help them to get services such as special schooling, mobility services, and even special health treatments. Specialist services, with their understanding and relationship with the voluntary organisations, are critical in helping patients and parents make contact with support groups and gain maximum benefit.

What is needed for effective care?

Effective care requires:

- making the correct diagnosis as quickly as possible
- instituting appropriate immediate therapy as soon as possible
- ensuring longer-term maintenance regimes are in place and being followed
- surveillance for possible complications and appropriate management
- prevention of complications which can cause death or further morbidity
- identification of family members at risk
- counselling and testing for family members

- identification of risks to pregnancy or fetus
- surveillance during pregnancy
- availability of counselling and antenatal genetic testing
- interdisciplinary work with and support from social services, education and voluntary organisations.

Effective services

We do not have systematic measures of outcome by which to judge the effectiveness of IMD services. However, some structural and process measures could act as proxies. Following discussion, we suggest that the following requirements would be important for providers to achieve effective services.

Structure

1. Availability of full specialist clinical and laboratory team to provide advice, support, and services for children, adolescents and adults
2. Clinicians and laboratory staff with appropriate level of specialist education and undertaking continuous professional development (CPD)
3. Adequate professional support
4. Professionals with adequate resources (including out-patient capacity) to undertake the necessary volume of work
5. Availability of full specialist clinical and laboratory team on a routine and emergency basis; and specialist services with formal relationships with the main feeder hospitals to provide diagnostic and management advice
6. Provision by specialist services of information on access to advice, testing and referral
7. Provision by specialist services of education to help non-specialists recognise IMDs and provide care appropriate to their level of expertise
8. Protocols for joint management and shared care to provide ongoing care and manage crises as far as possible
9. Arrangements for shared care to oversee long-term management and ensure referral back to specialist services at times of particular concern, such as during preparation for pregnancy and before surgical operations
10. Formal arrangements between specialist IMD team and genetic services
11. Formal arrangements between specialist team and a wide range of other specialties such as cardiology, renal, obstetrics and neurology
12. Full range of information to help patients make contact with relevant voluntary organisation
13. Active audit programme
14. Education and training programmes for specialists and other health professionals.

Process (activity)

15. Services should be undertaking the necessary volume of work to maintain sufficient experience across the breadth of IMDs.

Quality of care

Effectiveness is a vital element of high-quality services. However, there are other dimensions of quality that are important to professionals, patients and society as a whole. These include the following:

1. Efficiency. What is the most efficient way to deliver a specialist service? Is there some element of critical mass for efficient services?
2. Accessibility. Can patients get treatment when and where they need it? Are there barriers such as lack of information, distance, inability to pay, breakdown in service availability or waiting times?
3. Equity. Are there failings in equity? Are some groups of patients treated differently on the grounds of disease category, geography, age or ethnic group?
4. Relevance. Is the overall pattern and balance of services the best that could be achieved?
5. Acceptability. How is the service perceived by those who receive it (or might receive it)? Is it relevant, fair and responsive to demand? Is it what patients want and is it what professionals judge good practice?

These were key questions for us to address throughout the work, and they will be reported on further after the main reviews of services (see Chapter 11).

4 Review of laboratory services

Professor Anne Green, Lead Scientist, National Metabolic Biochemistry (Biochemical Genetics) Network

Executive summary

Current laboratory services for inherited metabolic disorders across the UK

1. **Test provision/repertoire**
   Workload volumes for core tests relate to populations served by individual laboratories; there is no evidence of significant underprovision or overprovision.

   There is a deficiency of acyl carnitine services for some laboratories.

   Some of the more specialist tests are vulnerable and a robust service is currently not provided.

   There are concerns about the potential impact of foundation hospitals on provision of the expensive very rare tests.

2. **Turnaround times**
   Turnaround times for routine core tests are significantly compromised in about 30 per cent of requests, owing to limited staff time and/or equipment failure.

3. **Out-of-hours services**
   There are no formal arrangements for emergency out-of-hours work, and *ad hoc* services are dependent on individuals being available and willing to help. There is a need for more formal back-up arrangements between laboratories.

4. **Accommodation for next five years**
   The following accommodation needs for the future for laboratory services require addressing:

   - 55 per cent of centres have inadequate laboratory accommodation
   - 75 per cent of centres have inadequate office accommodation.

5. **Equipment**
   Urgent replacement is required for 30 per cent of the amino acid analyzers (AAA) and replacement within three years is required for 50 per cent of AAA and gas chromatographs.

6. **Staffing / manpower planning**
   There are significant needs of additional scientists over the next five years to plan for retirements and new developments.

Diagnoses by laboratories

Data on diagnoses made by specialist laboratories in the UK suggest that 540–570 IMD diagnoses are made per annum. These data exclude some disorders, and therefore this is a minimum figure. The lack of databases means that this is an approximate figure.

Approximately 20 per cent of diagnoses are in adults.

For many patients there are no specialist clinical services to which referral may be made.

Recommendations

1. Increased manpower resources are required to ensure that very specialist tests are provided, to improve turnaround times and to provide out-of-hours services on a more formalised basis.
2. A greater capital investment in expensive specialist equipment is needed for new and replacement equipment – this should not be reliant on individual trust equipment programmes.
3. Continuation of investment in training for all health care scientists beyond the current three-year plan from the Department of Health's Genetics moneys is required.
4. There is a need to review accommodation requirements in the context of the overall plan for IMD services and newborn screening developments across the UK.
5. There is a need for laboratories to record all IMD diagnoses as part of a formalised database to enable service planning, monitoring and audit.

Acknowledgements

The Lead Scientist would like to thank colleagues in all stakeholder laboratories who have contributed to the provision of this data, and to Mary Dowling, Network Administrator, for compiling the report.

Stakeholder laboratories surveyed

Belfast	Royal Victoria Hospital
Birmingham	Birmingham Children's Hospital
Bristol	Bristol Royal Infirmary
Bristol	Southmead Hospital
Cambridge	Addenbrooke's Hospital
Cardiff	University Hospital of Wales
Edinburgh	Royal Hospital for Sick Children
Glasgow	Royal Hospital for Sick Children
Leeds	St James' University Hospital
Liverpool	Royal Liverpool Children's Hospital
London	Guy's Hospital
London	Great Ormond Street Hospital
Manchester	Willink Biochemical Genetics Unit
Manchester*	Royal Manchester Children's Hospital
Newcastle	Royal Victoria Infirmary
Sheffield	Sheffield Children's Hospital
Southampton	Southampton General Hospital

* *Specialist tests only – not included in core service analysis.*

Associate laboratories surveyed for the service review

London	National Hospital for Neurology and Neurosurgery
London	University College of London Hospital
Oxford	Department of Biochemistry, University of Oxford

St Helier Hospital, Carshalton, also completed the survey, but was not included in the analysis because it provides only a local service (population approximately 500,000).

1 Process

1.1 Service provision

In October to December 2003 an assessment (by questionnaire) of laboratory services was undertaken to obtain information on:

- current workload patterns
- development / future needs
- robustness of service.

There was a 100 per cent response; all 17 stakeholder laboratories responded (16 provide the core services). The survey provides data on manpower, equipment, accommodation and training. The data were compiled in February 2004. Selected summary data is provided in this document. A full report is available (metbionet@aol.com).

More extensive manpower data collection for the workforce review team was undertaken in May 2004.

1.2 Inherited metabolic disorders diagnoses

A second survey was undertaken by questionnaire in February 2005 to obtain data on IMD diagnoses. Data have been provided by 14 laboratories. There are no data on diagnoses from the Liverpool and Southampton laboratories.

2 Role of specialist laboratories

The specialist laboratories provide services for a core group of tests to diagnose and manage patients with the following groups of disorders:

- amino acids
- organic acids
- fat oxidation
- urea cycle
- carbohydrate.

Some of the laboratories include services for other disorders:

- peroxisomal
- mitochondrial
- lysosomal
- purine and pyrimidine.

The tests are largely chemically based, and include assays of metabolites and enzymes in body fluids and tissues. Some laboratories also provide selected molecular testing for IMDs to complement the other tests.

The laboratory role includes:

- advice on testing
- provision of specialist assays for diagnosis
- interpretation of results and further testing
- extended family testing
- prenatal diagnosis
- testing for management of the treatment and monitoring disease progression.

Staffing comprises consultant medical and consultant scientists who lead, direct and manage the laboratory service. The services in most centres are intimately linked with the newborn screening service, with shared accommodation, staff and equipment. The service is supported by highly specialised post-doctoral clinical scientists who specialise in specific areas. They are responsible for method selection and development, the quality and reporting of results and clinical liaison. Clinical scientists also participate in out-patient clinics and ward rounds as part of the multi-disciplinary IMD team. The clinical scientists are complemented by highly experienced biomedical scientists who undertake a large part of the specialist technical work. Both clinical scientists and biomedical scientists require specialist training and many years of experience before they are able to provide a clinical service.

3 Current service provision

3.1 Summary of laboratory size / population served (for 'core' tests) (n = 16)

Population	Number of laboratories
4 million or greater	5
3–3.9 million	2
2–2.9 million	6
1–1.9 million	3

3.2 Quality and accreditation

Fifteen out of sixteen laboratories are accredited with CPA UK Limited.

All laboratories participate in specialist External Quality Assessment (EQA) schemes where available; these are listed on the Metabolic Biochemistry website (www.metbio.net) against each laboratory entry.

A summary of EQA schemes for specialist assays is provided on the Network website.

3.3 Stakeholder laboratories providing core tests (n = 16)

Ammonia	16
Amino acids (plasma)	16
Amino acids (urine)	16
Organic acids	16
Acyl carnitines	9
Free fatty acids / 3-hydroxybutyrate	13
GAGs	14
Mono/Disaccharides	14

Conclusion

There is a deficiency in services for acyl carnitines in some areas. This is important because these tests are required urgently in some acute clinical situations.

3.5 Workload undertaken by stakeholder laboratories

Table 4.1 shows the number of requests made to UK laboratories per annum in relation to size of laboratory.

Table 4.1 Requests per annum

Population served (millions)	Amino acids	Urine Amino acids	Plasma Organic acids
1.4	–	–	648
1.5	470	380	540
1.6	560	840	492
1.75	–	–	702
2	800	650	1000
2	1200	800*	1800**
2	820	415	820
2.5	756	605	765
4	–	–	1800
4.5	1900	1000	2000
4.5	1750	500	1800
5.3	2163	687	2209
> 5			3714

* *3 million population.*

** *4 million population.*

Conclusion

The workloads correlate with the total populations served.

4 Specialist test repertoire (non-core)

For those tests that are non-core, the survey showed the following:

a. There are some redundant tests which could be dropped from the repertoire.
b. There is some overprovision of specialist tests (i.e. too many laboratories for some tests).
c. Many of the rarer tests are not easily available in the UK (i.e. need to refer specimens outside the UK).
d. There is a need for more molecular tests for IMD.
e. There is vulnerability for some specialist tests. For example, some enzyme assays are provided in one centre and/or are dependent on one or two individuals.

The network is currently addressing these issues via:

a. Enzyme working group – to advise on the specific areas which need improved provision.
b. UK Genetic Testing Network (UKGTN) for molecular tests – the network is contributing to the UKGTN.

4.1 Conclusion

There is a need to invest in the provision of the very rare tests to ensure robust provision for the future.

5 Turnaround times and robustness of service

5.1 Routine assays

Acceptable turnaround times for routine analyses are not met for a significant number of laboratories.

Table 4.2 Turnaround times: routine assays

Assay	Proportion achieved	Reasons
Amino acids	11/16	Batch size too small, equipment failure, clinical scientist time
Organic acids	10/14	Equipment, clinical scientist time
Acyl carnitines	5/8	Clinical scientist time

For approximately 30 per cent activity, turnaround times are compromised because of equipment failure and/or staff availability.

5.2 Emergency assays

Turnaround times are not met, as shown in Table 4.3.

Table 4.3 Turnaround times: emergency assays

Assay	Proportion achieved	Reasons
Amino acids	14/15	Equipment failure
Organic acids	12/14	Equipment failure, clinical scientist time

Conclusion

Some laboratories are unable to meet acceptable turnaround times for both routine and urgent assays, owing to instrument failures/shortage and/or staff availability.

6 Out-of-hours services

Most laboratories did not offer a formal out-of-hours analytical service; however, several provide an *ad hoc* service for some tests – by negotiation on a needs basis.

Thirteen laboratories provide an out-of-hours advisory service, as follows:

Formal duty biochemist	4
Consultant service	7 (1:1 or 1:2)
Ad hoc access	2

Conclusion

The out-of-hours advisory service is dependent on very few staff and on goodwill. There are no formal arrangements in place

7 Equipment needs

Several items of equipment are required in the next three years to meet service needs.

Amino acid analysers

- five required urgently (30% rigor mortis)
- ten required in the next three years.

Tandem mass spectrometers

- four required in next three years.

Gas chromatograph / mass spectrometer

- nine required in the next three years.

Conclusion

Capital for equipment purchase (new and replacement) at trust level is insufficient or not a priority.

8 Accommodation

Current position

Laboratories 12/14 – adequate
Office 8/14 – adequate

Future (next five years)

Laboratories 6/16 adequate and one with plans
Office 3/16 adequate and one with plans

Conclusion

For future needs:

- 55 per cent have inadequate laboratory accommodation
- 75 per cent have inadequate office space.

It is particularly important to address this, together with the development plans for newborn screening.

9 Staffing: current workforce for the laboratory IMD service (clinical scientists and consultant medical)

Table 4.4 Number of individuals (WTE)

	Consultants (medical and scientists)	Principal scientists	Senior scientists
Belfast	1 (0.8)	1 (1.0)	
Birmingham	2 (1.5)	4 (3.0)	2 (2.0)
Bristol Southmead	1 (0.4)	1 (0.9)	
Bristol Royal Infirmary		2 (2.0)	
Cambridge	1 (1.0)	1 (1.0)	
Cardiff	1 (0.2)	1 (0.5)	1 (0.8)
Edinburgh	1 (0.5)	1 (0.25)	1 (0.25)
Glasgow	2 (0.9)		3 (2.4)
Leeds	1 (0.9)		
Liverpool	1 (0.5)	1 (1.0)	1 (1.0)
London GOSH	1 (0.2)	2 (1.5)	2 (1.6)
London Guy's	2 (1.2)	1 (0.5)	3 (3.0)
London Guy's enzymes	1 (1.0)	1 (1.0)	2 (2.0)
London Guy's purines	1 (0.8)	1 (1.0)	2 (2.0)
Manchester	1 (1.0)	3 (3.0)	4 (3.05)
Newcastle	2 (1.0)	1 (0.4)	1 (0.9)
Sheffield	2 (1.2)	3 (2.8)	3 (2.7)
Southampton	1 (0.5)		
Total	**22 (13.6)**	**24 (19.85)**	**25 (21.7)**

Total number of scientists 71 (55.15)

These data exclude contributions to neonatal screening where stated, although the roles may often be shared / overlap.

The data exclude service contributions from trainees as these are difficult to assess. Specialist biomedical scientist staff are not included.

9.1 Workforce planning (for clinical scientists and biomedical scientists)

This was undertaken as a separate exercise for the Workforce Review team in May 2004 (separate report available). It includes planning for newborn screening developments.

Staff needs are estimated for the next five years for the UK (owing to retirements and additional developments, including newborn screening and training).

The recommended workforce needs are as follows:	
Clinical scientist consultants and principal posts	49
Number of posts per year across the UK	10
Biomedical scientists:	
Chief and senior (Grade 3 and 4 posts)	46
Number of posts per year across the UK	9

These data assume 25 per cent attrition rate and some individuals taking up posts in the less specialised centres.

10 Training

10.1 Clinical scientists

Clinical scientist staff function as consultants or principal scientists and require training to MRCPath level, plus higher specialist training (HST) in metabolic biochemistry. Until recently there were no training posts. With funding from Department of Health Genetics, additional trainee clinical scientists have been appointed to new HST posts. Eleven individuals are in post across England. (Note that these plans cover England only.)

Although these current plans are addressing training needs, there are concerns from within the profession that there will be a gap at the higher level for a few years whilst this present cohort of trainees complete their training. There are also no on-going plans for training posts.

10.2 Biomedical scientists

There is a need to establish training posts for biomedical scientists to provide the specialist technical training required for the delivery of the service. This would ideally be linked with a vocational MSc module in Metabolic Biochemistry. Currently no such formalised training exists and training is on the job.

10.3 Trainers

Insufficient trainer time was a major issue, and has now been addressed via the Network with DH Genetics funding. A lead trainer and cluster trainers in three sites have been appointed across England with Genetics White Paper funding for three years.

There are also increased training demands on the laboratories arising from the specialist registrars in metabolic medicine and other specialist areas such as genetics.

Limited space for training purposes is also an issue for some laboratories.

10.4 Conclusions

There is a need to engage with the Workforce Development Directorate to plan manpower requirements beyond this first intake of additional clinical scientist trainees, and specifically to plan and develop more formalised training for biochemical scientists.

11 IMD diagnoses

Data on the total diagnoses made by the specialist laboratories for their 'regional' population have been collated and related to the population served. There will be some bias because some laboratories have a special interest and specialise in certain tests.

Table 4.5 Total diagnoses

Laboratory	Approximate population (millions)	Diagnoses per million population
Belfast	1.6	6.3
Birmingham	5.2	20.6
Bristol Royal Hospital & Southmead	3.8	8.4
Cambridge	2.2	4.5
Leeds	4.5	7.5
London Guy's	4.0	8.5
London GOSH	10.0	9.1
Manchester**	4.5	*
Newcastle	2.5	5.6
Sheffield	4.2	7.1
Cardiff	2.0	7.5
Glasgow	3.0	7.3
Edinburgh	2.2	7.7
Total	**45.2**	**~9.2** (total no diagnoses 416 a year)

* *Diagnoses are averaged over the last two- to four-year periods (i.e. 2001–2004/5) where available. An estimate for PKU diagnosed from newborn screening has been added where not provided.*

** *Data available for lysosomal disorders only – therefore not included.*

11.1 Total diagnoses across UK pro rata

Approximately 540 diagnoses per annum (over the last four years) when extrapolated to whole of UK (58.8 million)

Total diagnoses reported by UK laboratories:
2003/4 573

These are cumulative total diagnoses not related to population for all laboratories providing data, but this total excludes some data from:

- Northwest (Manchester and Liverpool)
- Wessex
- Oxfordshire/Northamptonshire/Berkshire.

There are clearly problems in making such extrapolations:

- There is likely to be some double counting, such as for confirmatory tests sent away on the same patient and some diagnoses not recorded.
- Diagnoses arising from newborn screening may not have been included in some returns.

- Not all specialist laboratories have been included; for example numbers of diagnoses have not been provided for
  - porphyrias
  - neurotransmitters
  - oxalurias
  - trace metal disorders.
- Hyperlipidaemia diagnoses are not included.
- The survey will not have captured some diagnoses where the diagnosis is made by molecular tests, such as for mitochondrial disorders.

Conclusion

There is a need for laboratories to record diagnoses as part of a formal database to enable planning of services, monitoring and audit.

12 Diagnoses and predicted incidence for groups of disorders

12.1 Estimated incidence

Table 4.6 Predicted incidence

	Total number of cases per annum*	Estimated total UK cases per annum*	Estimated incidence
Amino acids	75	155	1:5,000
Urea CD	12	25	1:32,000
Organic acids	43	89	1:9,000
Fat oxidation	51	106	1:7,500
Carbohydrate**	50	103	1:7,500
LSD (pop. 36.6m)	67	108	1:7,300
Perox***	30		
Mito***	21		
Purine/Pyr***	15		

* *Average of 2002 and 2003 in 11 laboratories covering population of ~ 28 million.*
** *Includes GSD.*
*** *Probably includes supra-regional or national services, so cannot extrapolate.*

12.2 Age at diagnosis

The list below shows that, although most cases were diagnosed in the paediatric age group, around 20 per cent are diagnosed in adults:

< 10 years	72%
10–16 years	7%
>16 years	21%

13 Referral of diagnosed patients by laboratories

Laboratories were asked to state to where patients were referred. Comments are as follows:

- Birmingham: no adult service to refer to; some go to neurology, hepatology or stay in a renal clinic
- Bristol: 65 per cent of paediatric cases referred to a non-metabolic paediatrician

- Cambridge: 25 per cent non-metabolic referral
- Cardiff: 100 per cent metabolic referral
- Leeds: no data provided
- Newcastle: 100 per cent metabolic referral
- Sheffield: all patients can be offered specialist paediatric or adult metabolic referral; shared care arrangements often undertaken
- Glasgow: 47 per cent non-metabolic referral
- Edinburgh: 29 per cent referred to metabolic paediatrician – rest unknown; some may have died, others single speciality referral
- London Guy's: no data provided
- London Guy's purine laboratory: 90 per cent non-metabolic referral

Conclusion

In a number of centres (Birmingham, Bristol, Cambridge, Glasgow and Edinburgh) some patients diagnosed from laboratory testing are not able to be referred to specialist services for management of their condition.

5 Survey of inherited metabolic diseases services

1 Introduction

The purpose of the survey was to identify the main providers of specialist IMD services in the UK and obtain details of the services offered, structure of services and activity; and any information on service shortfall.

2 Method

The main services were identified by individuals in the stakeholder group. An initial introductory letter signed by Dr Graham Shortland was sent to each service identified, asking them to clarify what services were provided in their area and to nominate an individual who would take responsibility for completing the questionnaire on behalf of the centre. Services were followed up by email and telephone message on 25 February. Full questionnaires were sent to named individuals in March 2005. Where further services were identified by word of mouth or through circulation of draft work, they were also invited to submit evidence or, at least, outline information on the main structure of services and activity. This survey was complemented by a laboratory survey undertaken separately by the National Metabolic Biochemistry (Biochemical Genetics) Network (www.metbio.net).

3 Centres identified and contacted

A total of 24 providers of some specialist IMD services were identified. All completed detailed questionnaires: 18 in England, providing services in London and 9 other cities in England (Newcastle upon Tyne, Manchester, Liverpool, Leeds, Bradford, Sheffield, Birmingham, Cambridge and Bristol), 1 city in Wales (Cardiff), 4 in Scotland (Edinburgh, Glasgow, Aberdeen and Dundee) and 1 in Northern Ireland (Belfast). Twenty returned detailed questionnaires and the remaining four returned outline information, in one case through a telephone interview. Details of questionnaires distributed and respondents are given in Appendix 5.1. This represented a return from every provider of specialist services identified in the UK.

4 Outline of services available in main geographical regions

Providers of some level of specialist service who responded to the survey are listed below by geographical region. It is of concern that there are no providers in the East Midlands region.

Table 5.1 Outline of services provided on a regional basis

Region	Services identified
Northeast	Royal Victoria Infirmary, Newcastle upon Tyne School of Clinical Medical Sciences, Newcastle upon Tyne
Northwest	Manchester Lysosomal Storage Disorder service Manchester Willink Biochemical Genetics Unit Royal Liverpool Children's Hospital, Alder Hey
Yorkshire and Humber	St Luke's Hospital, Bradford Northern General Hospital, Sheffield Sheffield Children's NHS Trust Leeds General Infirmary

East Midlands	No services identified
West Midlands	Birmingham Children's Hospital
Eastern	Cambridge University Teaching Hospital (Addenbrooke's Hospital)
London & Southeast	London Guy's Hospital London Royal Free Hospital London Great Ormond Street Hospital for Children London University College Hospital
Southwest	Bristol Royal Hospital for Children North Bristol NHS Trust, Southmead Hospital
Wales	University Hospital of Wales, Cardiff
Scotland	Royal Hospital for Sick Children, Edinburgh West of Scotland Royal Hospital for Sick Children, Glasgow Royal Aberdeen Children' s Hospital Ninewells Hospital and Medical School, Dundee
Northern Ireland	Northern Ireland Regional Services for Inherited Metabolic Diseases, Royal Group of Hospitals Trust, Belfast

It can be seen that there are providers of IMD services spread throughout the UK, with the exception of in the East Midlands, where there is no service. (Note: since the completion of the survey we have been notified that there is a small and limited service at Leicester). **However, the degree to which they provide comprehensive services is highly variable. This is detailed throughout the report and summarised in Table 14.** A brief description of each of the services is given in Appendix 5.1.

5 Structure of services

5.1 Age group

Seven services were formally provided for adults and children, though in a number of children's services there were arrangements for adults to be seen as there was nowhere else for them to go. In three further locations there was formal coordination of separate adult and paediatric services, and in one other location there were separate services but with less formal coordination. In five centres outside London there were paediatric services only, and in one centre (Leeds) there were adult services only, though here an outreach children's service was provided from Manchester. In all other centres provision was less coordinated and more fragmentary, often based primarily around paediatric services that had expanded to continue to care for children who reached adulthood and for whom no other service was available. Table 5.2 gives details.

Table 5.2 Target age group for services

Centres	Age group
Newcastle children and adults	Distinct services with informal links in one district
Manchester LSD Service	Adult and paediatric
Manchester Willink	Adult and paediatric
Liverpool	Adult and paediatric
Leeds	Adult only
Bradford	Paediatric (some adults seen)
Sheffield children and adults	Distinct services coordinated in one district
Birmingham	Paediatric with limited adult out-patient service; most adults provided for within the paediatric facilities
Cambridge children and adults	Distinct services coordinated in one district
London Guy's	Adult and paediatric
London Royal Free	Adult and adolescent
London GOSH	Paediatric only
London UCH	Adults and adolescents
Bristol Royal Hospital for Children	Paediatric only
Bristol Southmead	Adult and paediatric
Cardiff	Paediatric only
Edinburgh	Paediatric only
Glasgow	Distinct services coordinated in one district
Aberdeen	Paediatric only
Dundee	Adult and paediatric
Belfast	Adult and paediatric

5.2 Links between adult, paediatric and laboratory services

Nearly all of the services/centres reported good, close links between all elements of the service present in that location. In ten locations this was formalised through joint clinics; regular meetings with formal consultation attended by adult, paediatric and laboratory services; and wider multi-disciplinary team meetings in which individual patients, investigations and results were discussed. In four services it was reported that links with laboratories were created and strengthened considerably by clinical consultants working within the laboratory and by close location of the facilities, or that the laboratory consultant ran the clinical service.

5.3 Links with other specialties

Ten services reported extensive formalised links with a wide range of other specialties. This represented the four London centres and six other services throughout England (Birmingham, Cambridge adult and child, Manchester, Sheffield adult, Newcastle adult). The range of services included cardiology, nephrology, hepatology and liver transplant, surgery, ENT, haematology and bone marrow transplant services, neurology, neurosurgery, endocrinology, dermatology, ophthalmology, genetics, lipid services, metabolic bone services and obstetrics. These links were formalised through joint clinics, regular meetings to discuss patients, and formal provision of specialist services through a named consultant or department.

In other services, links were either not described or were less formalised, based sometimes on personal interest or individuals working across services, or were made for individual patients or families on a case-by-case basis through cross-referral. As services were in main teaching hospitals, it was usually possible to make referrals to a wide range of other specialties.

5.4 Genetics input into services

The genetics input into the IMD services was generally reported as working very well. This tended to work through attendance at joint clinics or joint meetings, or through informal and formal clinical interactions (see Table 5.5 for summary). In particular, close working was reported by a number of services where diagnostic genotyping was an important element of the service, for example in Gaucher disease or mutational analysis for PKU. In some cases the close liaison was supported by genetics laboratories being co-located with metabolic biochemistry laboratories. In three cases, one of the genetics consultants was designated as having a special interest in IMDs. Other services described less formal arrangements in which individual patients were referred to genetics as appropriate.

Table 5.3 gives detailed comments on the arrangements made for specialist genetic input into services.

Table 5.3 Comments on arrangements for genetics input

Centres	Genetics input
Newcastle children	Genetics service does not designate anyone as having a special interest in IMD; cases tend to be picked up geographically
Newcastle adult	Named consultant adult geneticist provides input through quarterly joint metabolic genetics clinic and direct referral pathway
Manchester Willink	Combined clinics where necessary; close liaison with genetics laboratory at Central Manchester (within the same trust)
Leeds	Named geneticist
Bradford	Patients seen in Bradford by Leeds team
Sheffield adult	Direct referral from clinical genetics into the service
Sheffield children	Genetics, clinical and biochemical laboratory services all accommodated together
Birmingham	Geneticists have monthly clinics and attend IMD patient meetings once a month and the weekly neuro-metabolic clinic; joint business meetings including clinical and laboratory group and geneticists once every three months
Cambridge child	Close informal relationship with genetics team
Cambridge adult	Referral of patients and close interaction for molecular diagnosis where diagnostic genotyping, e.g. Gaucher disease
London Guy's	Weekly meetings, direct liaison for genotyping, enzyme laboratory

	part of genetics, counselling and prenatal tests organised by genetics
London Royal Free	Clinical and diagnostic support through regional genetics service; in-house availability for genetic counselling; some in-house molecular diagnostic services available; prenatal testing referred to regional genetics service
London GOSH	Joint consultations, weekly ward round, follow-up genetic counselling, genetic tests in diagnosis
London UCH	Clinical genetics are separate but provide occasional advice; use neurogenetics laboratory and molecular genetics laboratory at GOSH as needed
Bristol Royal Hospital for Children	Works very well, with good liaison between genetics department and IMD consultant
Bristol Southmead	Individual patients/families referred as appropriate for genetic counselling; support for antenatal diagnosis and some intra-partum treatments
Cardiff	Dedicated geneticist for liaison
Edinburgh	Not described
Glasgow	Close working as department of Genetics runs the neonatal screening programme; Clinical Genetics staff link with midwifery and obstetric staff in genetic counselling and antenatal diagnosis related to IMD
Aberdeen	Not described
Dundee	Informal and formal clinical and laboratory interactions
Belfast	Cross-referral of clinical cases as appropriate to a group of four clinical geneticists; mutational analysis for PKU carried out in Regional Clinical Genetics department (Belfast City Hospital); mutational analyses of other conditions sent to appropriate national laboratory

5.5 Links with peripheral hospitals

Ten services provided formal outreach support to DGHs within their region and beyond. This included London services and services at Cambridge, Manchester, Sheffield, Newcastle upon Tyne and Dundee. Three LSD services reported formal shared care arrangements for patients to receive care from local providers. In other centres provision of support within the region was less formal, including running an annual symposium and being available for out-of-hours consultation and referrals from colleagues.

Table 5.4 Formal links with peripheral hospitals

Newcastle children	Clinics in Sunderland, Stockton and Middlesbrough
Newcastle adult	None
Manchester LSD Service	Formal links with home provider or satellite centre for therapy
Manchester Willink	Provide metabolic outreach service for Alder Hey (Liverpool), Leeds, Bradford and Airedale
Liverpool	No information
Leeds	None
Bradford	None
Sheffield adult	Clinics at Doncaster
Sheffield children	Clinics at Barnsley, Rotherham

Birmingham	Some shared care arrangements with other hospitals but no formal outreach clinics
Cambridge child	Outreach clinics at Norfolk and Norwich Hospital
Cambridge adult	Formal shared care with local providers for LSD and formal arrangements for home therapy
London Guy's	Outreach clinics: London KCH, Portsmouth, Plymouth, Norwich, Brighton and abroad; shared care with local hospitals
London Royal Free	Formal shared care arrangements with local hospitals for LSDs; formal arrangements for home therapy services
London GOSH	Outreach clinics at Reading and Bristol
London UCH	None
Bristol Royal Hospital for Children	None
Bristol Southmead	None
Cardiff	Annual symposium
Edinburgh	None
Glasgow	None
Aberdeen	None
Dundee	Perth
Belfast	No formal links (all patients within 100 miles of Belfast)

5.6 *Commissioning arrangements*

Ten services were able to describe formal commissioning arrangements. In three services this was known to be through some sort of regional specialist services commissioning; in other services it was known to be via the PCTs or through a parent directorate such as acute medicine or general metabolic services; and in three services the NSCAG contracts were quoted as being part of the commissioning arrangements. In Northern Ireland commissioning was through the Regional Medical Specialties Committee. The Cambridge service at Addenbrooke's Hospital reported having a dedicated commissioning support team. Other services reported that commissioning arrangements were under discussion. Details of responses are given in Table 5.5. **It is important to remember that this represents the understanding of those providing the service and not necessarily the commissioners.**

Table 5.5 Arrangements for commissioning

Centres	
Newcastle children	Not known
Newcastle adult	Not yet formalised – under local review
Manchester LSD Service	NSCAG funding for LSDs
Manchester Willink	Not known
Liverpool	Not described
Leeds	None
Bradford	No separate arrangements; attempts underway to agree commissioning arrangements including local tariffs
Sheffield children	Specialised Services Commissioning arrangements through the North Derbyshire, South Yorkshire and Bassetlaw Commissioning Consortium

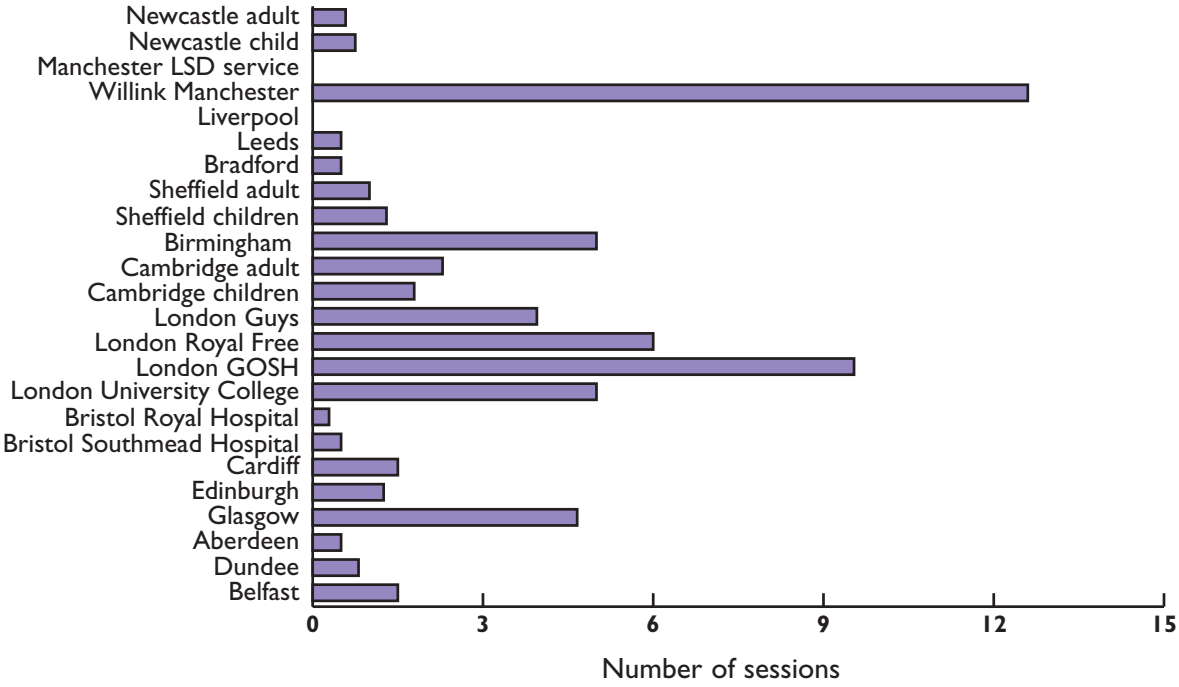
Sheffield adult	Through parent directorate (Acute Medicine Sheffield Teaching Hospitals) to PCTs
Birmingham	Through West Midlands Specialist Services Agency (Clinical and Laboratory)
Cambridge children	Dedicated commissioning support team; NSCAG designation for LSD; regional commissioning of general metabolic service to be reviewed 2005/6
Cambridge adult	Dedicated commissioning support team
London Guy's	Via PCTs; formal bid for NSCAG approval submitted
London Royal Free	NSCAG funding/designation for LSDs service and drug costs, with commissioning support for these services through the service performance team
London GOSH	No response
London UCH	NSCAG funding for LSDs
Bristol Royal Hospital for Children	None
Bristol Southmead	None
Cardiff	Currently under negotiation with Health Commission Wales (service does not have own budget)
Edinburgh	None
Glasgow	Scotland has no designated national service; no commissioning arrangements
Aberdeen	Not described
Dundee	Informal discussion, formal referrals
Belfast	Through Regional Medical Specialties Committee

5.7 Out-patient sessions

Average number of sessions

Services were asked to give information on numbers of dedicated out-patient sessions at main centre and any peripheral hospitals. This is summarised in Figure 5.1. In only 14 centres was the total more than an average of one session per week. Seven services provided four or more out-patient sessions per week. London Royal Free provides six formal clinic sessions and operates an open-door policy during weekdays for patients with Gaucher or Fabry disease and day-care services from Monday to Friday. The vast majority of these services were provided at the main hospital, with services at peripheral clinics being characteristically only once or twice per year.

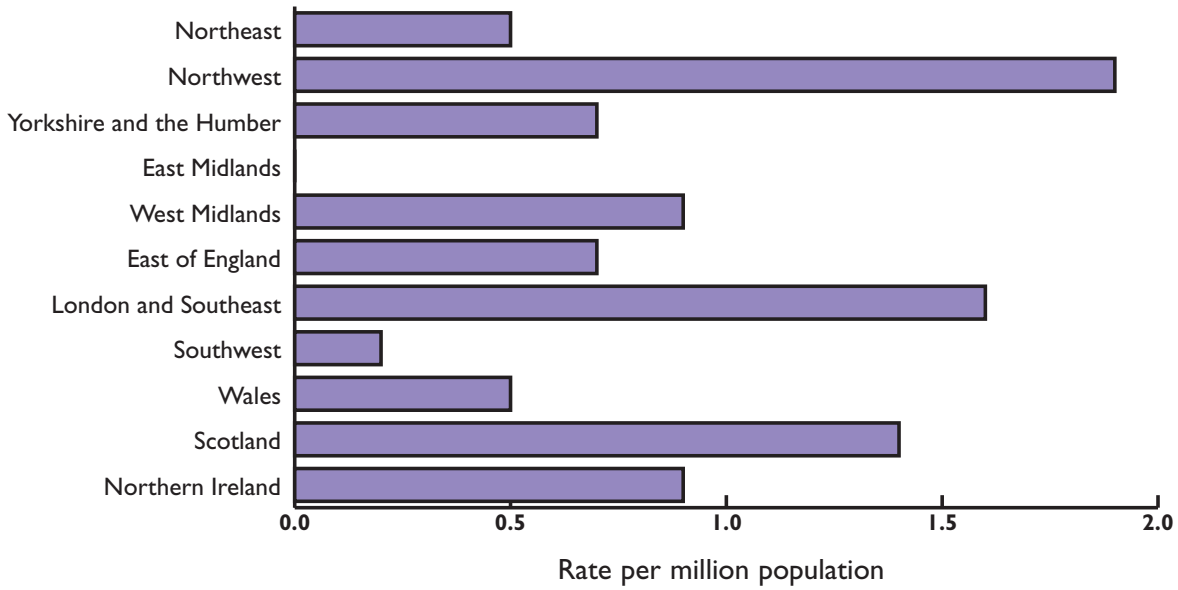
Figure 5.1 Total average number of out-patient sessions per week



Regional comparisons

The total average weekly provision of out-patient sessions varies widely across UK regions, with an almost ten-fold variation from 0.2 sessions per million population in the Southwest to 1.9 in the Northwest region (see Figure 5.2). A table of regional populations is given in Appendix 4 to this report.

Figure 5.2 Total average number of out-patient sessions per week in geographical region per million population



5.8 Clinical staffing

Services were asked to give information on the clinical workforce of medical, nursing and dietetic staff and any other staff involved in the care of patients with IMDs. Services also gave information on laboratory staffing, details of which are presented in Chapter 4. It is clear that in all services consultant clinical biochemists and other senior scientists are close and integral members of the multi-disciplinary team. Most laboratories are also responsible for the neonatal screening service,

with some staff being dedicated to this aspect of the work. They are then able to integrate diagnoses arising from the screening services with specialist clinical work and ensure a seamless patient journey.

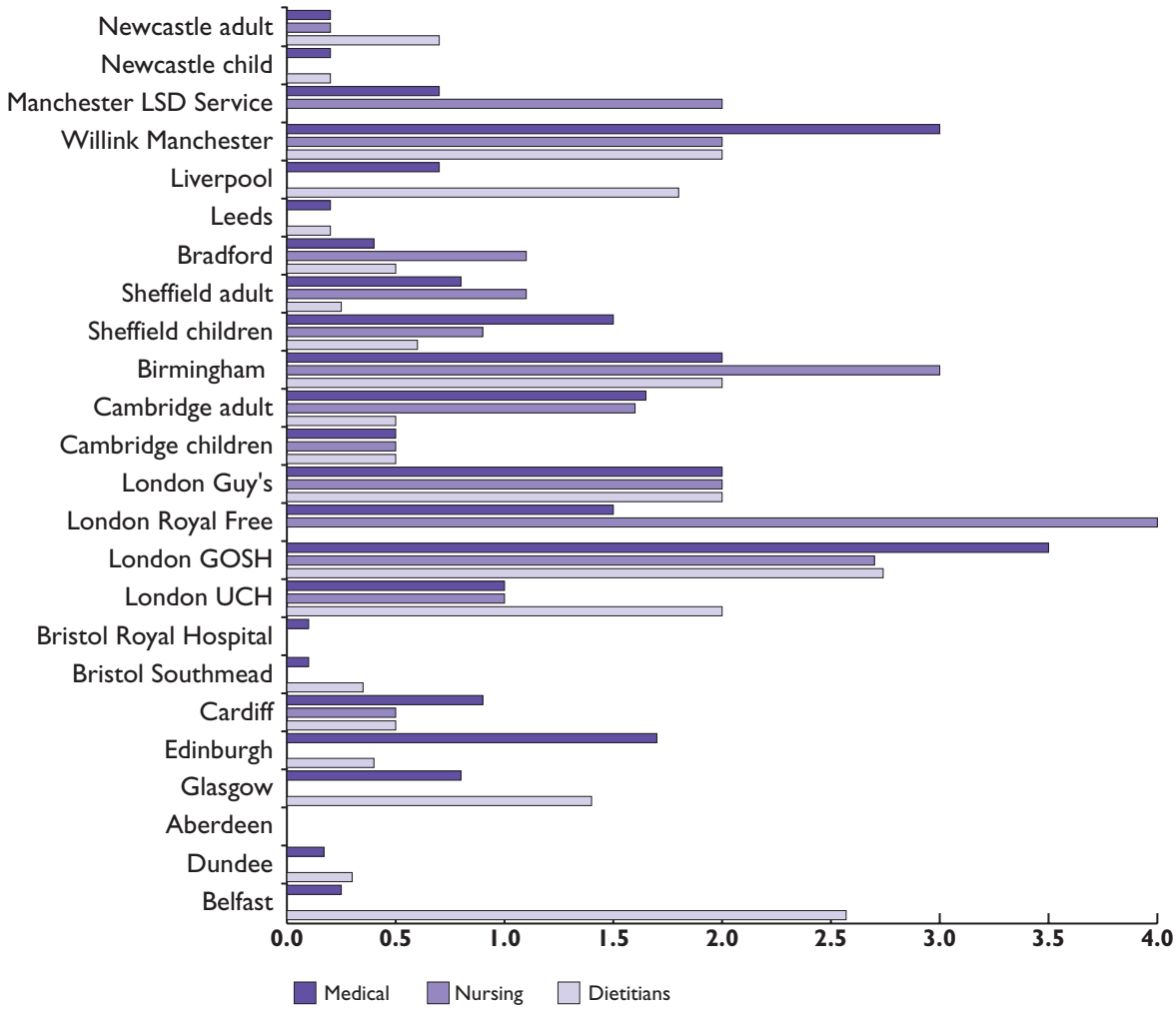
Table 5.6 shows that across the country there are just over twenty WTE provided in each of the three main disciplines concerned in specialist provision: namely medical, nursing and dietetics. This is provided by a total of 46 medical consultants, 29 specialist nurses and 35 dietitians. This represented respectively 52 per cent, 78 per cent and 61 per cent of total time available from medical, nursing and dietetic staff. Because a higher proportion of the staff employed in the main London centres were full-time, this meant that outside the main centres the average percentage time spent on IMDs is less than this.

Table 5.6 Total IMD specialist workforce

Total IMD workforce			
	Medical	Nursing	Dietitian
Total WTE	23.87	22.6	21.51
Total individuals	46	29	35
% time spent on IMD	52	78	61

Figure 5.3 gives summaries of the staffing available in the various services.

Figure 5.3 Clinical workforce in IMD (WTE)

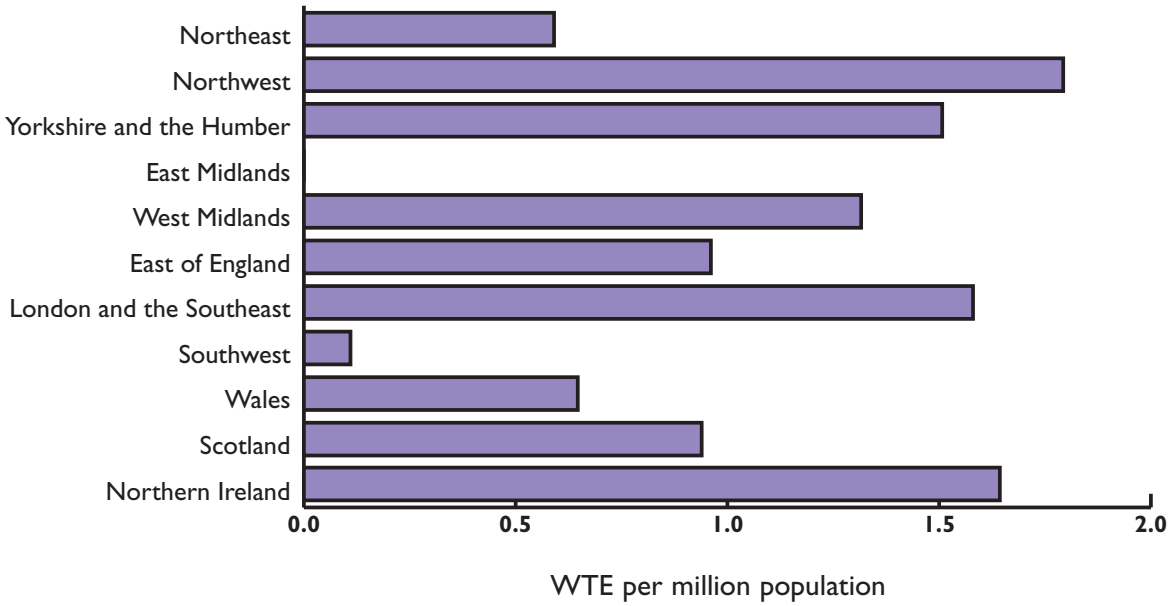


The following points may be noted:

- In only two centres (Manchester Willink, London GOSH) were there at least three WTE medical staff, and in a further three services (Cambridge adult, Sheffield adult, Edinburgh) there were three individuals involved in provision of medical care – that is, enough to provide a very basic rota of care.
- There are 13 services with a whole multi-disciplinary team: Birmingham, Cambridge adult, Cambridge children, Cardiff, London Guy's, London Royal Free, London GOSH, London UCH (Charles Dent), Manchester Willink, Newcastle adult, Sheffield adult and children, Bradford.
- In only five centres (only Birmingham and Manchester outside London) was there at least one WTE of each multi-disciplinary team member.
- Although there are a number of individuals working in IMDs in various centres across the country, their input to the service in terms of WTE is often very limited.
- In nine centres in England and in all centres outside England the total input of medical staff is less than 1 WTE.
- In some centres, part of the clinical workforce is used in screening programmes and follow-up; for example, in the Birmingham service the clinical nurses are 1.5 WTE for screening follow-up and 1.5 WTE clinical IMDs.

Comparison of total staffing in geographical regions shows huge disparity across the UK (see Figure 5.4). The total clinical staff per million population varies from 0.11 in the Southwest to 1.8 in the Northwest.

Figure 5.4 Total clinical workforce by region (WTE per million population)



In addition to these core clinical staff, the staff shown in Table 5.7 were reported by centres.

Table 5.7 Additional staff reported by individual services

Consultant posts	
Birmingham	Vacant
Belfast	Planned for two years' time
Training posts	
Specialist registrars	Birmingham, Cambridge adult and children, Cardiff, London Guy's, London GOSH, London UCH (Charles Dent), Manchester Willink, Belfast
Senior house officer	Cambridge children
Research nurses	Cambridge adult, London Guy's, London GOSH, London UCH (Charles Dent), London Royal Free
Other	
Psychologist	Belfast service also employs a psychologist 0.6 WTE who is present at paediatric clinics, supervises routine IQ tests and is seen as essential in helping with behavioural problems in this patient group London Royal Free has access to clinical/educational psychologist for adolescent and adult patients with Gaucher or Fabry disease; two haematology counsellors also cover LSDs
Social worker	Belfast: social worker 0.1 is also assigned to the service Birmingham: also has funding for a link worker, pharmacy and psychology support London Royal Free: access via Patient Advice and Liaison Service

6 Activity in IMD services

6.1 Numbers of patients and attendances

Services were asked to give information on the number of patients currently attending clinics (known and being followed up by the service) and annual numbers of new and follow-up attendances, with breakdown by age (paediatric or adult), condition and geographical location where possible. In some cases numbers given were approximate; other services, such as London UCH, had information on patient registers; and some services (notably Birmingham, Sheffield and Manchester) were able to give accurate information from hospital activity analysis. Total figures are given in Table 5.8.

More than ten thousand patients were looked after in the services, about two thirds of these being children. (Some services were unable to give a breakdown of numbers of patients by age; in these cases numbers were attributed to the main care category – this was usually the paediatric service, although it is acknowledged that some of the patients cared for in these clinics will be adolescents or adults – or split two thirds to one third child/adult for services that care for both.) The annual number of new referrals varied from 6 to 250 with a median of 34.

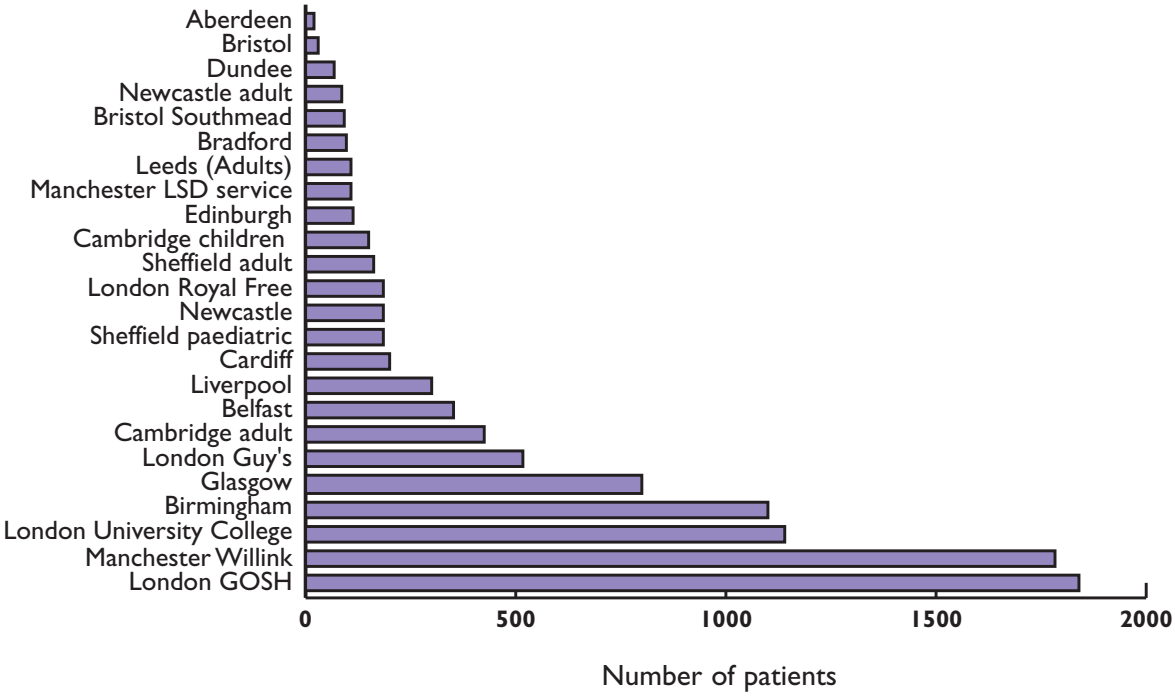
Table 5.8 Activity reported by centres

Centres	Total patients*	Children	Adult	New referrals	Follow-up
Newcastle adult	86	0	86	13	
Newcastle children	185	185	0	20	400
Manchester LSD Service	108	11	97		
Manchester Willink	1783	1207	576	238	1488
Liverpool	300	200	100		
Leeds adult	108	0	108	No info	No info
Bradford	97	78	19		260
Sheffield adult	162	0	162	20	151
Sheffield children	185	185		47	217
Birmingham	1100	803	297	100	800
Cambridge children	150	150		34	225
Cambridge adult	425	0	425		1100
London Guy's	517	445	72	128	659
London Royal Free	185	2	183		544
London GOSH	1840	1840		250	
London UCH	1140		1140	118	1260
Bristol Royal Hospital	30	30		25	No info
Bristol Southmead	92	57	35	6	120
Cardiff	200	150	50	50	600
Edinburgh	113	77	36	20	180
Glasgow	800	800		60	850
Aberdeen	20	20			
Dundee	68	55	13	6	210
Belfast	352	252	100	20	900
Total	**10046**	**6547**	**3499**	**1155**	**9964**

* The total number of patients looked after by the service, or on the service database or register.

Figure 5.5 shows a ranking of services by total number of patients attending, varying from 20 to 1,840 with a median of 185. It may be seen that only five services care for seven hundred patients or more. (This number was thought by the stakeholder group to represent an approximate critical number for whom comprehensive services could be efficiently provided.)

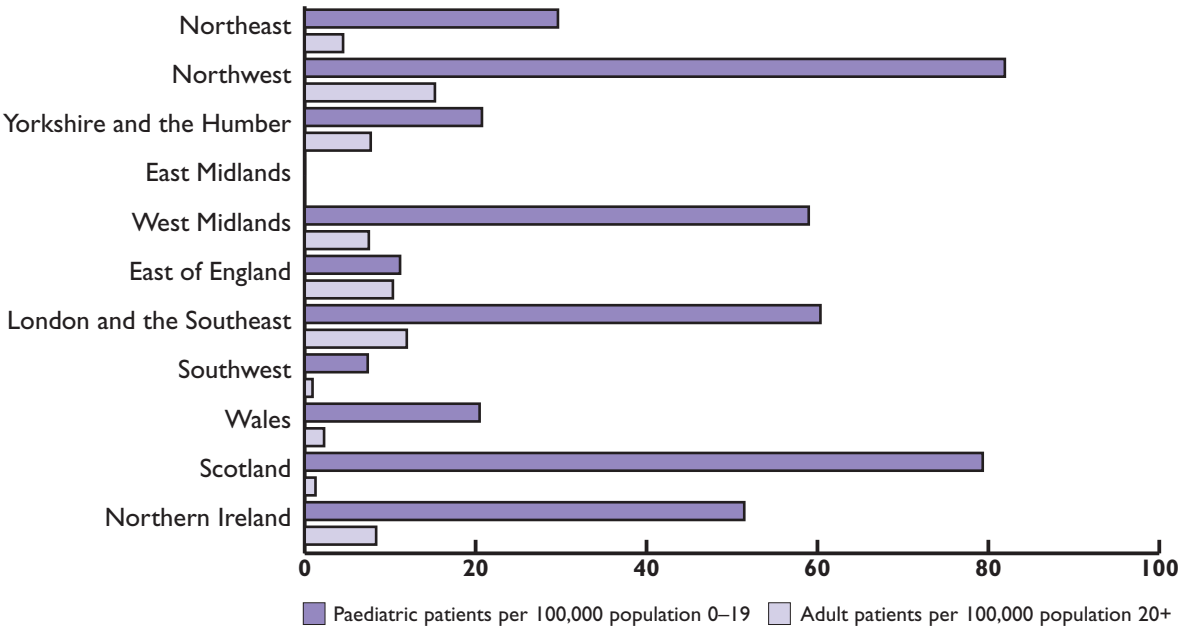
Figure 5.5 Ranking of IMD services by number of patients attending



6.2 *Rates and possible shortfall*

Regional rates of patients attending specialist centres were calculated, based on Government Office regions in England and Wales and population statistics for Scotland and Northern Ireland. The population group for child was 0–19 as children with disabilities are often included in paediatric services up to the age of 19. Rates varied from 82.0 per 100,000 child and 15.2 per 100,000 adult in the Northwest to 7.4 per 100,000 and just under 0.9 per 100,000 adult in the Southwest. (Note that some of the patients from the Southwest and other services may be attending London services and other major centres.) Comparative regional rates are shown in Figure 5.6.

Figure 5.6 Regional rates for attendance at specialist centres per 100,000 population



If rates of attendance in the Northwest were found across the UK as a whole, it might be expected that more than 12,000 children and more than 6,800 adults would be in contact with services. Given then the number of patients attending services shown in Table 5.9, a possible shortfall of nearly 6,000 children and almost 3,500 adults can be estimated.

Table 5.9 Estimates of possible UK shortfall of patients attending specialist services

	Children	Adults
Estimated number for UK*	12103	6827
Totals reported	6547	3499
Estimated shortfall	5556	3328

* Based on rates for Northwest region

6.3 Trends in activity

Eight services were able to give information on trends in activity. These are summarised in Table 5.10.

Table 5.10 Trends in activity

Centres		99/00	00/1	01/2	02/3	03/4	04/5	% increase (lowest to highest)
Manchester Willink	New referrals		148	171	191	245		66
Bradford	New referrals**	16	24	28	31			94
Sheffield adult	Total attendances	74	90	124	144	165		123
Sheffield children	New referrals		7	21			47	571
Birmingham*	New referrals		24	34	51	67		179
London UCH (Charles Dent)	New referrals	75	75	90	96	118		57
London Guy's	New referrals	83	111	84	109	103	124	49
London Royal Free		70		133		185		164
	Follow-up		1413	1371	1450	1486		5

* Paediatric and screening referrals only; will not capture adult referrals.
** Actual diagnoses.

Several services (e.g. London Guy's, Sheffield and Cambridge) also reported marked increases in referrals on appointment of initial or subsequent IMD consultants. Cardiff reported that there has been a 450 per cent increase in dietetic services for IMD.

6.4 Disease categories managed

Nine services were able to give detailed information on the disease groups into which their patients fell (see Table 5.11). A further five could give limited information – characteristically, they knew the number of patients who had PKU and little more. The other services gave no information on disease breakdown. The most common condition treated was PKU, followed by LSDs, diseases of carbohydrate metabolism and lipid disorders.

Table 5.11 Breakdown of patients attending services by disease

Centres		Amino acid	Urea cycle	Carbohydrate	Organic acid	Glycogen storage	LSD	Fatty acid oxidation	Peroxisomal	Mitochondrial	Lipid disorders	General /0ther
Newcastle children	N											
Newcastle adult	Y	44	3	5	3	4	19					
Manchester Willink	Y	229		41		38	15			21		
Leeds	N											
Bradford	Y	30	8	8	5	4	13					29
Sheffield adult	N											
Sheffield children	L	34									17	134
Birmingham	L	300										
Cambridge children	N											
Cambridge adult	N											
London Guy's	Y	180	18	46	20	23	11	39		46	57	82
London Royal Free	Y						185					
London GOSH	Y	175	48	50	75	40	145	79	20	50	75	200
London UCH	Y	397		45		67	55				66	410
Bristol Royal	N											
Bristol Southmead	L	75	5									
Cardiff	L	60										
Edinburgh	Y	46	2	6	9		6	10	2	4	1	
Glasgow	N											
Aberdeen	Y	13			2							5
Dundee	N											
Belfast	L	254			5							98
Total		1700	84	201	114	176	439	128	22	121	159	953

Key: Information available Y= Yes, L = limited, N = No

6.5 Audit

Services were asked for information on recent audits they had undertaken in IMD. Fourteen services were undertaking some audit, most frequently around PKU control (see Table 5.12).

Table 5.12 Audit activity reported

Bristol Royal	None
Newcastle children	None on IMD
Newcastle adult	B12 deficiency in PKU populatio
Manchester Willink	Regional PKU audit, laboratory QA
Leeds	None
Sheffield adult	
Sheffield children	
Birmingham	Inpatient and out-patient activity and ethnicity; extensive and formal audit programme including follow-up from newborn screening, investigation and treatment protocols, e.g. GSD and tyrosinaemia
Cambridge children	Ongoing audit of existing services; will be actively involved in audit of LSDs
Cambridge adult	Immunisation and antimicrobial prophylaxis audit of Gaucher disease patients with splenectomy; Osseus, adverse complications of Gaucher Therapeutic delivery of ERT
London Guy's	Rolling audit of PKU against MRC standards, and others on PKU (comparison of centralised and non-centralised service)
London Royal Free	Extensive research and audit in Fabry and Gaucher disease; patient satisfaction survey; home therapy v. hospital therapy survey; quality of life survey
London GOSH	
London UCH	PKU compliance with diet, homocystinuria metabolic control, galactosaemia bone density and neuropsychometric outcome
Bristol Southmead	Regional audit of newly diagnosed PKU
Cardiff	PKU audit of services (Manchester, Melbourne, Birmingham)
Edinburgh	PKU level of metabolic contro
Glasgow	Informal audit of PKU service
Aberdeen	
Dundee	Outcome of newborn screening programme and management and control of patients with PKU
Belfast	Control of PKU, effect of less strict diet after eight years on IQ change between 8 and 18 years, pregnancy outcome in maternal PKU

7 Evidence of unmet need

Services were asked to give evidence of adult patients looked after in paediatric settings, patients lost to follow-up, problems arising from lack of referral to specialist care and any other evidence of unmet need. In general, respondents were concerned that a specialist IMD service should be available to all patients with IMDs, but frequently was not. In addition, specialist advice should be available to colleagues outside the regional centre, in other specialties such as Regional Paediatric Intensive Care Unit (PICU) (Bristol), obstetrics (Newcastle, Glasgow, Edinburgh) and the National Screening Programme centres (Bristol, Sheffield).

The most robust evidence came from those centres able to document some 831 adult patients looked after in paediatric settings. Lack of national and local records has made it very difficult to document patients lost to follow-up, but services described patients 'turning up' or being referred back from DGHs with problems, during pregnancy, with mental health problems, or simply when consultants lost interest in them. Patients also seemed to find specialist services by chance, and there was a general feeling that many patients were simply being looked after in DGHs where there was lack of specialist medical, nursing and dietetic advice. Services were also concerned that they had to turn away patients who were from outside their geographical area (even though they might have been within the region), because they did not have sufficient capacity (particularly dietetic advice), or because the time to wait for an appointment was too long. A number of services were concerned that they were unable to give sufficient time to their patients to provide optimal care. This was particularly noted in failure to achieve acceptable metabolic control in PKU.

The lack of clinical medical, nursing and dietetic time made services very vulnerable to staff changes, and a number of services noted concerns with regard to succession planning or cover for annual leave or staff development. Laboratory staffing is a major issue to ensure provision of the very specialist assays required for the service (see Chapter 4).

Lack of nursing or dietetic support was mentioned by Bristol, Cambridge adult, Leeds, Manchester and Dundee. Other services commented that there was no time to train and educate dietitians and nurses who might be developed to provide further support to the service. Sometimes specialist clinics were provided without support from specialist dietitians.

Many services commented that difficulties would get worse as more and more patients were referred as a result of increased screening. For example, this was noted in the Sheffield return, where there have been an increasing number of new diagnoses as a result of the pilot MCADD newborn screening programme.

Other themes included the availability of clinical time to provide a proper regional service. Many centres were acutely aware that they were not providing a regional service. They were not commissioned to provide a regional service – for example, Bristol provided only the metabolic service to the city, with patients elsewhere in the region being looked after in their own DGH or referred to London. This meant that some patients had long travelling distances. In Newcastle upon Tyne the service was not recognised as a regional service and so there was 'no scope for local delivery of care'. In Cambridge it was noted that there was no regional network that could support more local care; and in Scotland, notably Aberdeen, there were problems of remoteness. All this meant that consultants and other specialists needed to be available informally for out-of-hours advice – with resulting problems of providing such cover at times of annual leave or other absences.

Services were aware of the need to develop the provision of specialist IMD support throughout their region, through developing shared care arrangements; providing education and support to local colleagues including health, educational and social service professionals; and participating in case conferences (Belfast). However, as well as lack of funding, pressure of everyday work left them little time to be proactive in undertaking new initiatives, to develop the necessary resources or protocols, or to review service design and delivery.

Services wanted to be able to provide more support to patients and their families by making home visits, training them to provide care for themselves at home, training local staff to provide care nearer the patient's home, and developing more education and information for patients and their families.

Pressures on the service also left little time for their own staff development – to attend conferences or study days, or to undertake audit of research.

The availability of services for in-patient management required for investigation, day procedures and for acute decompensation was mentioned as a problem by Birmingham, London Guy's (lack of neonatal beds for non-ventilated premature babies), London GOSH (to accept urgent referrals) and London UCH.

The full range of comments on unmet need is given in Appendix 5.3.

8 Overview and conclusions

Information has been provided about IMD services in 24 trusts throughout the UK. This represents a complete response from the services identified.

8.1 Assessment of need

A total of 10,046 patients were identified as receiving care specialist care; 6,547 (63%) children and 3,499 (37%) adults. This represents a UK rate of 16.9 per 100,000 population

The Northwest is the only UK region that could be said to provide reasonably comprehensive services to a regional population. The rates for patients attending specialist services here are 81 per 100,000 child and 15.2 per 100,000 adult.

If this rate were applied to the UK population as a whole, we would expect a total of approximately 12,100 children and 6,800 adults to be in contact with services. Thus there is likely to a shortfall of some 5,600 children and 3,300 adults with IMDs who are not in contact with specialist services.

8.2 Provision of comprehensive services

A total of 24 providers of IMD services were identified across the UK. However, the degree to which they provide comprehensive services is highly variable. (The Manchester lysosomal service only provides national specialist services for these conditions and so is not included further in this analysis). Following discussion in the stakeholder group, Table 5.13 shows some of the critical criteria for a comprehensive service, listed with a point rating according the degree to which each criterion was met. The criteria were grouped into broadly clinical (maximum 24 points) and broadly organisational (maximum 6 points). Individual services were then scored against these criteria, and the results are given in Table 5.14 with services grouped according to health service region.

Table 5.13 Key to rating factors

Clinical areas (maximum 24 points)	Description	Rating
Specialist **workforce**	At least 3 WTE medical staff	***
	At least 3 individuals involved in the provision of medical care	**
	At least 1 WTE each of medical, nursing and dietitian	**
	Complete multi-disciplinary team	*
Number of **out-patient clinics**	More than 4 per week	**
	1–4 per week	*
Involved in provision of coordinated **adult/paediatric** services	Dual provision or involved in formal arrangements	***
	Informal arrangements	**
	Paediatric clinics also provide some care for adults	*
Integration of **laboratory** service	Totally integrated service with multi-disciplinary team meetings at least weekly	***
	Regular formal multi-disciplinary team meetings involving laboratory but less than weekly	**
	Good working relationship but not formalised	*
Outreach services or shared care arrangements	Formal arrangements	***
Links with other **specialist** services	Extensive and formalised	***
	Limited formal arrangements	**
	As required	*
Number of patients	700 or more	***
	200–699	**
	50–199	*
Able to provide information on **disease categories**	Yes	**
	Limited	*
Undertaking **audit** in IMD	Yes	*
Organisational areas (maximum 6 points)		
Geographical provision	National or provision of a regional service	***
	A wider defined geographical population (e.g. a number of PCT areas)	**
	Provision to local population	*
Formal **commissioning** arrangements	National or regional specialist commissioning	***
	Commissioned under other formal arrangements	**
	Commissioning under discussion	*

Table 5.14 Overview of services

	CLINICAL PROVISION									ORGANISATIONAL		
Centres	**Workforce**	**OP clinics**	**Adult/ paediatric**	**Lab. links**	**Specialist links**	**Number of patients**	**Outreach**	**Disease categories**	**Audit**	**Geographic**	**Commissioning**	**Total (30)**
Newcastle children			**	**No info**	*	*	***			**		**9**
Newcastle adult	*		**	***	***	*		**	*	**	*	**16**
Manchester Willink	****	**	***	***	***	***	***	**	*	***	**No info**	**27**
Liverpool		**No info**	***	**No info**		**				**	**No info**	**7**
Leeds				***	*	*				**		**7**
Bradford	*		*	*	**	*		**		*	*	**10**
Sheffield adult	***	*	***	**	***	*	***			*	**	**19**
Sheffield children	*	*	***	***		*	***	*		**	***	**18**
Birmingham	***	**	*	***	***	***		*	**	***	***	**23**
Cambridge children	*	*	***	**	***	*	***		*	***	***	**21**
Cambridge adult	***	*	***	**	***	**	***		*	***	***	**24**
London Guy's	**	**	***	***	***	**	***	**	*	***	***	**27**
London Royal Free		**	***	***	***	*	***	**	*	***	***	**22**
London GOSH	****	**	***	***	***	***	***	**	**No info**	***	**No info**	**26**
London UCH	**	**	***	*	***	***	***	**	*	***	***	**26**
Bristol Royal				*	**					*		**4**
Bristol Southmead			***	*	*	*		*	*	*		**9**
Cardiff	*	*	***	**	**	**		*	*	**	*	**16**
Edinburgh	***	*		**	**	*		**	*	**		**14**
Glasgow		**	***	***	*	***			*	**		**14**
Aberdeen				**No info**				**		**		**4**
Dundee			***	*	*	*	***		*	**		**12**
Belfast		*	***	***	**	***		*	*	***	***	**20**

Manchester Willink and London GOSH are the only centres that achieve the full rating for comprehensive clinical services in UK. (These centres lost points only because they could not, or did not, provide information on commissioning processes for the services.)

Out of the maximum of 30 points, services may be grouped as follows:

21–30 Mancheter Willink, Birmingham; Cambridge children and adult, London Guy's, London Royal Free, London GOSH, London UCH

11–20 Newcastle adult, Sheffield adult and children, Cardiff, Edinburgh, Glasgow, Dundee, Belfast

0–10 Newcastle children (very little information provided), Leeds, Bradford, Bristol Royal, Bristol Southmead, Aberdeen.

The following regions did not have a service in the top category: Northeast, Yorkshire and Humber, Southwest, Scotland, Northern Ireland. Apart from East Midlands, where there was no service, the region with the most deficient service was Southwest, where services rated in the bottom category only.

8.3 Regional services

The only regional services are Northwest, West Midlands, Eastern, London and Southeast, and Northern Ireland. Other regions must address this deficiency as a matter of urgency.

8.4 Adult services

Many services do not have adequate provision for paediatric patients as they reach adolescence and adulthood. Severe gaps in adult services are noted in West Midlands, Southwest and some Scottish services. The present situation of adults attending paediatric services is unacceptable and must be rectified by development of new services with specialist expertise and capacity to take on adult IMD patients.

8.5 Clinical capacity: workforce and clinic time

Most services do not include a full multi-disciplinary team provided at a level able to cope with the necessary volume of work including out-of-hours provision. This capacity must be developed for all IMD services offering core provision. However, across the country it was notable that consultants were anxious to undertake more sessions in IMD if these services could be funded, and so it is clear that extra expert clinical capacity is available to be commissioned.

Out-patient provision is extremely small in many regions, proving a major constraint on the numbers of patients who could be seen and particularly long waits in some centres for tertiary referrals and follow-up appointments. The huge disparities in service provision across the country must be addressed.

Increasing demand

Many centres reported increasing pressure on services. Some were able to document this in rising numbers of patients known to the service or increasing numbers of referrals. Others noted more patients being referred as new consultants were employed or new services developed. Numbers will continue to increase because of:

- new disorders and/or sider phenotypes being described and new tests becoming available
- greater awareness
- further diagnoses made as a result of extended newborn screening (currently in pilot phase but possibly to be implemented further in UK)

- increasing expertise and standards for long-term specialist management of patients
- more children surviving to adulthood as a result of ERT and other therapies.

Numbers of patients must continue to be monitored and services designed to cope with increasing numbers.

8.6 Integration with other specialist services

IMD services need to be closely integrated with a wide range of other specialist services. Only the major services had formalised arrangements such as joint clinics, joint clinical and pathology meetings and input from named consultants. In other cases this was less formalised – though as most were in major teaching centres the opportunity for referral of patients to specialist services was usually available, although long waiting times for tertiary referrals were reported.

8.7 Developing local networks

Many services have limited capacity to develop and support peripheral hospitals in undertaking care for patients on a shared basis. Developing this would provide extra support for services whilst enabling specialist care to be delivered to patients near to their home, wherever necessary.

Main recommendations

1. Specialist commissioners and providers must discuss and agree overall configurations of services so that centres and/or networks are able to provide services to an agreed regional population and covering the entire UK between them.

2. The absence (East Midlands) and extreme deficiency (Southwest) of services in some regions must be addressed as a matter of urgency.

3. The lack of adult services in West Midlands, Southwest and some Scottish services must be addressed as a matter of urgency.

4. Initially providers should come together on a regional or supra-regional basis to ensure that they can provide the following for their populations:
   - Coordinated and integrated paediatric, adult and laboratory services.
   - A critical mass of professionals as multi-disciplinary team to provide 24-hour care and to ensure robustness and continuity of services. This should include laboratory, medical, nursing and dietetic professionals immediately with expansion to include pharmacy and psychologists when possible.
   - Formal arrangements with supporting tertiary specialties to provide wider specialist expertise.
   - Arrangements for tertiary services to support district general hospitals.
   - Education and training for all groups of specialist professionals, those providing specialist care in other specialties, and, as appropriate for secondary and primary care providers.
   - Clinical and laboratory databases to monitor and audit.
   - Supporting information to commissioners.

5. Commissioners and providers will need to plan for an expansion of clinical services to double approximately across the UK in order to cope with current unmet need. This should be kept under review in the light of:
   - numbers of trends in numbers of new cases reported by the specialist laboratories
   - findings of the pilot studies on extended newborn screening and policies of the National Screening Committee to extend this further
   - expert guidance based on understanding of the outcomes of new tests and treatments.

Appendix 5.1 Details of IMD services contacted

Services	Name of informant	Status
School of Clinical Medical Sciences (Child Health) Newcastle upon Tyne	Dr George Rylance	Discussion
Royal Victoria Infirmary, Newcastle upon Tyne (adult service)	Dr Nicky Leech	Returned
Manchester Lysomal Storage Disorder Service	Ms Lorraine Thompson	Outline
Royal Manchester Children's Hospital, Willink Biochemical Genetics Unit	Dr John Walter	Returned*
Liverpool	Ms Tricia Rutherford	Outline
Leeds General Infirmary	Dr Janet Horner	Returned
St Luke's Hospital, Bradford	Dr Geoff Lealman	Returned
Northern General Hospital, Sheffield, Adult Inherited Metabolic Disorders Clinic	Dr Godfrey Gillett	Returned
Sheffield Children's NHS Trust, Paediatric Metabolics	Dr Mark Sharrard	Returned
Clinical IMD Department, Birmingham Children's Hospital	Dr Anupam Chakrapani	Returned*
Cambridge University Teaching Hospital (Addenbrooke's Hospital), Paediatric metabolic service	Dr Uma Ramaswami	Returned
Cambridge University Teaching Hospital (Addenbrooke's Hospital), Adult metabolic service	Dr Patrick Deegan	Returned
London Guy's Hospital, Department of Paediatric and Metabolic Medicine	Dr Michael Champion	Returned
London Royal Free Hospital, Lysosomal Storage Disorders Unit	Ms Sian Goodwin	Returned
London Great Ormond Street Hospital for Children, NHS Trust	Professor Peter Clayton, Dr Maureen Cleary	Returned
London University College Hospital, (Charles Dent Metabolic Unit)	Dr Philip Lee	Returned
Bristol Royal Hospital for Children	Dr Julian Hamilton Shield	Returned
North Bristol NHS Trust, Southmead Hospital	Dr Michael Webster	Returned
University Hospital of Wales, Cardiff, Paediatric and adult metabolic medicine	Dr Graham Shortland	Returned*
Royal Hospital for Sick Children, Edinburgh	Dr David Fitzpatrick	Returned*
West of Scotland (GCHB) Royal Hospital for Sick Children/Queen Mother's Hospital/ Glasgow Royal Infirmary	Dr Peter Robinson	Returned
Royal Aberdeen Children's Hospital, Aberdeen	Dr Iain Auchterlonie	Outline
Ninewells Hospital and Medical School, Dundee	Professor Robert Hume	Returned
Northern Ireland Regional Services for Inherited Metabolic Diseases, Royal Group of Hospitals Trust, Belfast	Professor Elizabeth Trimble	Returned

* Denotes supplementary material sent

Appendix 5.2 Outline of services

Services	
Newcastle	Separate children and adults' services provided, with some outreach to peripheral hospitals by children's service. Planned transition from paediatric to adult service. Limited medical input, small amount of nursing and dietetic input. Adult service officially a local service, but adults from across Northeast region treated. Some research in PKU and galactosaemia (children).
Manchester Lysosomal Storage Disorders Service	Provides a family-centred approach to the management and treatment for adults and children from Northeast and Northwest England, Scotland, North Wales and Northern Ireland. ERT for adult Fabry disease provided at Hope Hospital site, while therapy for children initiated 2 miles away within Willink department at Pendlebury Children's Hospital. All therapy is transferred to a homecare provider or satellite centre in partnership with families, and management of care continues to be provided from the Hope Hospital site.
Manchester Willink Biochemical Genetics Unit	Comprehensive clinical and laboratory supra-regional service for patients with inborn errors of metabolism. Includes purpose-built out-patient unit, a laboratory and 4-bedded research unit. Provides service to Northwest and beyond through outreach to peripheral hospitals. Designated specialist centre for lysosomal disorders [CHECK]. Major research programmes in ERT in LSDs and cord blood screening programme.
Liverpool	Provides in-patient and out-patient services to paediatric and adult patients from North Wales, Merseyside, Cheshire and Isle of Man.
Leeds	Limited service aimed at adults with varied case mix. Some patients attend across Leeds boundary.
Sheffield adult	Service for adults with any metabolic disorder. Started in January 1999, based in endocrine investigation unit with 2 specialist nurses shared between endocrine and metabolic work. Recently moved to general out-patient department. Serves defined population in South Yorkshire metropolitan area. Some outreach and good links with relevant specialties.
Sheffield paediatric	Provides paediatric metabolic services for North Trent and further south and neonatal screening to Trent region. Peripheral clinics in Barnsley and Rotherham. Participates in national MCADD research project and QA.
Birmingham	Birmingham Children's Hospital provides multi-disciplinary services for the diagnosis, treatment and management of patients with entire range of IMDs for West Midlands region. Some shared care arrangements with local paediatricians, but currently no outreach clinics Services also accessed by surrounding regions. Limited service for adults with some disorders provided at University Trust (Queen Elizabeth Hospital). Research programmes in newborn screening, dietary management and enzyme replacement therapies.
Cambridge paediatric	Referral centre for metabolic disease in Eastern region and an NSCAG designated service for LSDs. Provides out-patient and inpatient service with close links with other teaching hospital specialties. Research programme related to LSDs in children.
Cambridge adult	One of NSCAG designated centres for management of LSDs concerned with clinical care and research on these disorders, but also with interest in porphyrias, hereditary fructose intolerance and disorders of iron

	overload. Located in major teaching hospital. Formalised relationship with paediatric service for LSDs on same hospital site.
London Guy's	Provides regional metabolic service for South Thames for both adult and paediatric patients with IMDs. Research programmes in newborn screening, Tay Sachs, purine and pyrimidine disorders and hepatocyte transplantation.
London Royal Free	NSCAG designated centre for LSDs with significant research interests in pathophysiology and treatment of Gaucher and Fabry disease. Also provides metabolic and genetic services for specific conditions within department of haematology.
London GOSH	Large paediatric metabolic unit and NSCAG designated service for LSDs. Manages children with all metabolic disorders and provides very specialised and intensive service including dietetics, intensive care, haemofiltrations and dialysis, peritoneal dialysis, bone marrow, renal and cardiac transplantation. Many major research programmes.
London UCH	Service for adolescents and adults with all inherited metabolic disorders; NSCAG designation for LSDs. Close links with paediatric service at London GOSH. Adolescent lipid clinic. Research programmes in glycogen storage diseases, PKU, ERT and adrenomyeloneuropathy.
Bristol Royal Hospital	Bristol Royal Hospital for Children is tertiary referral hospital for whole of Southwest, also takes many patients from South Wales. One consultant provides a metabolic opinion, mainly entailing consultation, advice and treatment of children with inherited metabolic disease in the tertiary PICU at Bristol Children's and NICU at St Michael's Hospital. Research programme on fatty acid oxidation and glucose metabolism.
Bristol Southmead	Service provided by single-handed consultant doing 2 clinics a month and working the rest of the time in a DGH 50 miles away. Clinic is mainly for PKU children and adults, serves largely the Bristol area. Throughout rest of region individual DGH paediatricians and teams manage own patients with referral to other specialist centres as they feel is needed. Laboratory research in peroxisomal disorders.
Cardiff	General metabolic service (all disorders) providing in-patient and out-patient care for adult and paediatric patients in South and Mid Wales. Research in PKU and porphyria.
Edinburgh	Full service for diagnosis and management of children with IMDs but lack of transition and adult services. Major research programme at MRC Human Genetics Unit on disorders of fatty acid oxidation and sterol biosynthesis.
Glasgow	Paediatric and adult services provided at hospitals in Glasgow. Services provided in liaison with obstetrics for pregnant women with IMDs. Small trials of commercial dietary products.
Aberdeen	Service provided by consultant in medical paediatrics with special interest in metabolic medicine who provides single-handed specialty cover in this and other areas, and with a part-time dietitian.
Dundee	Limited service provided in tertiary centre by single-handed consultant in paediatrics, with support from part-time dietitian. Research programme in genetic and developmental regulation of early human metabolism.
Belfast	Comprehensive service for biochemical diagnosis and monitoring, and clinical management of adults and children and neonatal screening, from single centre. Full coverage of IMD except Gaucher disease. Research programme in bone density in PKU.

Appendix 5.3 Comments on unmet need

Newcastle adult	Historically PKU patients not seen in joint obstetric/medical clinic setting, thus problems with communication with obstetric team. Recently developed joint approach and liaison midwife. Service not yet recognised as regional service, therefore no scope for local delivery of care. Not funded for inevitable expansion. Need for increase in dietetic availability.
Manchester	Adults with PKU from outside clinic not being accepted owing to lack of sufficient dietetic support. Lack of specialist laboratory support – difficulty in maintaining service and developing new assays.
Leeds	Referrals returned because of insufficient dietetic support.
Bradford	The unmet need is the lack of funding, not the patients or the expertise to manage their conditions.
Sheffield children	Ability to deliver care locally and give support to local professionals and family. Education, home visits, develop shared care. Need to respond to new cases arising from extended newborn screening. Enhance research, development and audit.
Sheffield adult	Inadequate dietary support. Some patients lost to follow-up because of reluctance to travel from periphery to centre. Largely single-handed service with difficulty arranging cover when consultant on leave. Bid for part-time adult dietetic post has been submitted annually but not funded.
Birmingham	Major difficulties with in-patient management of adults with IMD, e.g. for investigation, day procedures and acute decompensation. Long out-patient waits for follow-up and tertiary referrals owing to lack of capacity.
Cambridge children	Some local DGHs manage adult PKU patients and liaise with paediatric metabolic physicians from London.. Essential that specialised metabolic services are provided by centres with expertise in paediatric IMD.
Cambridge adult	No regional network, insufficient dietetic expertise over wide region. Succession and continuity requirements for clinical and diagnostic service are a matter of urgent concern and have implications for training and recruitment opportunities.
London Guy's	Late referrals for maternal PKU as previously lost to follow-up in another region. Lack of neonatal beds in London, especially for non-ventilated premature babies with suspected IMDs. Demand for patient information far exceeds time available to write it – time consuming but essential. Increasing numbers of graduates from paediatric service. Constant financial pressures for service developments as IMDs are always competing with other services with greater patient numbers. NSCAG for LSDs being limited to a small number of centres may stunt development of newer services. Need for further expansion of consultant number to provide the additional clinics and expand current ones.

London GOSH	Need for more in-patient beds to accept urgent referrals, need for increased dietetic support.
London UCH	Many referrals have taken a long time before they have found an adult centred service – often found through serendipity. Lack of a second consultant. Difficulty in obtaining in-patient beds in an emergency.
Bristol Royal Hospital	Need dedicated full-time inherited metabolic disease consultant with back-up facilities of a dedicated full-time dietitian and possibly a half-time nurse – urgent unmet need that could provide a regional service.
Bristol Southmead	No data for adults managed within their own local DGH throughout the rest of the region – suspect mixture of adult and paediatric care and some who drop out of care completely. Women referred to Bristol service are primarily young women considering pregnancy. No data on patients lost to follow-up. Failure to achieve acceptable metabolic control, e.g. PKU. Families attending small units do not have specialist dietitians or medical staff. Not updated on new products for diet and sometimes inappropriate advice on diet in response to levels, age, growth, etc. Women referred in pregnancy often unaware of what is needed. Time to diagnosis due to referral out of region of routine tests, notably acyl carnitine analysis. Non-PKU patients have to travel long distances (London, Manchester, Birmingham). No trained specialist metabolic input for regional PICU on neonatal unit. Limited specialist advice available to screening service. Future: need to support National Programme Centre newborn screening standards – at present not able to reach them, e.g. for home visits at diagnosis by dietitians and nurse specialists. Likely further concern when MCADD introduced in next 2–3 years.
Cardiff	Growing gap between staffing levels and clinical workload has created a situation where post holder has to prioritise patient interventions. Patients not provided with the level of care that their condition dictates. Due to workload pressures, no time to train dietetic colleagues – implications for cover (only basic cover available). One third of IMD clinics do not receive dietetic support and succession planning. Time delays in delivering optimal service. Limited development of resources and protocols, absence of audit and research to improve patient care. Limited attendance at relevant study days / conferences to update skills and knowledge. Unable to undertake service appraisal to review service design and delivery. No funding for nurse or psychologist support.
Glasgow	Age of transfer from paediatric service can be at least 19 years, and sometimes for complex cases hard to find adult specialist to take them on. Many adult PKU cases lost to follow-up.

	Pre-pregnancy dietary control in PKU only about 60 per cent despite contact and educational events. Worryingly loose arrangements for other diseases (e.g. urea cycle disorders, organic acidaemias in pregnancy). Lack of national database means patients are unknown to the services and can present in crisis in labour or puerperium.
Edinburgh	Service potentially fragile due to main consultant's research commitments. No formal links with antenatal services for care of pregnant patients with PKU. Lack of cross-cover for PICU in Scotland is a concern. Lack of coordinated approach to emergency care protocols and integrated care pathways.
Aberdeen	Problems of remoteness and small numbers. Single consultant needs to be available informally for out-of-hours advice. Succession planning.
Dundee	Psychology sessions difficult to obtain. Specialist nurse input. Dietitian sessions need to increase. Vulnerability of medical and laboratory staffing due to staff changes.
Belfast	Difficulty in supporting patients with PKU in the community by providing adequate support to case conferences, etc.

Appendix 5.4 Estimates of rates of patients attending specialist IMD services

	Population 0–19 1000s	Population 20+ 1000s	Number of patients		Rate per 100,000	
			Children	Adults	Children	Adult
Northeast	624.3	1915.1	185	86	29.6	4.5
Northwest	1730.8	5073.7	1418	773	81.9	15.2
Yorkshire and the Humber	1268	3741.3	263	289	20.7	7.7
East Midlands	1052.2	3200.1			0.0	0.0
West Midlands	1361.5	3958.4	803	297	59.0	7.5
East of England	1344.2	4118.7	150	425	11.2	10.3
London and Southeast	3789.5	11678.7	2287	1395	60.4	11.9
Southwest	1179.8	3819.5	87	35	7.4	0.9
Wales	732.9	2205.1	150	50	20.5	2.3
Scotland	1199.9	3878.5	952	49	79.3	1.3
Northern Ireland	489.9	220.4	252	100	46.9	11.2

Sources - Office of National Statistics Mid-2003 Population Estimates: Quinary age groups and sex for local authorities in England and Wales; estimated resident population

Registrar General for Scotland. Mid 2004 population estimates

The Northern Ireland Statistics and Research Agency. General Register Office Mid year estimates, 2004

6 Services for patients with porphyria

Dr Michael Badminton, Director, Cardiff SAS Porphyria Service

Introduction

The porphyrias are a group of inherited disorders of haem biosynthesis that present with acute attacks, cutaneous photosensitivity or, in some cases, both (Table 6.1). Of the seven disorders, only three present in childhood: erythropoietic protoporphyria (EPP) and the two rare autosomal recessive conditions, congenital erythropoietic porphyria (CEP) and ALA dehydratase deficiency porphyria (ADP). The majority of patients present during adulthood, and specialist clinical and diagnostic services have therefore not been delivered via the paediatric metabolic network, but rather from adult services developed within academic departments with a particular clinical and laboratory interest in the porphyrias. As there has been no formal planning of specialised services in the UK, when senior staff retire or resign these units are frequently forced to close due to lack of expertise, staff or funding. The most well-known example is the closure of the Glasgow Porphyria Service, with the consequent loss of all patient records.

Background

Four porphyrias may give rise to acute attacks, which require admission to hospital and may be recurrent. There is a significant associated morbidity and mortality; we are aware of four deaths from acute porphyria within the last 12 months in the UK. Three acute porphyrias are autosomal dominant conditions in which presentation before puberty is exceptionally rare. The prevalence of acute attacks has been estimated as 1–2 per 100,000, but clinical penetrance is low. The most common acute porphyria is AIP, and studies on blood donors suggest that about 1 in 1,700 of the population carry an AIP gene. It is not possible to predict which of these individuals are most at risk of acute attacks, and current practice focuses on presymptomatic diagnosis and providing patients with information about the condition and how to minimise risk. New treatments under evaluation for severely affected patients include liver transplantation and enzyme replacement therapy (ERT).

Patients with acute porphyria are managed by a wide variety of different specialists – including dermatologists, haematologists, geneticists, neurologists, gastroenterologists, paediatricians and endocrinologists – but very few doctors see more than one or two patients during their professional career. There is wide variability in clinical practice, with patients frequently complaining that their clinician is unable to answer questions relating to management, prognosis or family counselling.

The cutaneous porphyrias present with two types of skin lesion: skin fragility and blistering (bullous porphyrias) or acute photosensitivity (EPP). Most patients are referred to a dermatologist, in many cases a photodermatologist with experience in this group of disorders. Dermatologists require access to a specialised laboratory to identify the type of porphyria as treatments differ for each type. Most clinical biochemistry laboratories lack the equipment and expertise to screen for cutaneous porphyrias, and misunderstanding and incorrect sample analysis are well-known causes of delayed diagnosis, particularly of EPP.

Table 6.1 The porphyrias

Porphyria	Enzyme	Inheritance	Prevalence*	Clinical
ALA dehydratase deficiency porphyria (ADP)	ALA dehydratase	AR	Unknown	Acute attacks
Acute intermittent porphyria (AIP)	Hydroxymethylbilane synthase	AD	1–2:100,000	Acute attacks
Congenital erythropoietic porphyria (CEP)	Uroporphyrinogen III synthase	AR	<1:106	Photosensitivity (bullous)
Porphyria cutanea tarda (PCT)	Uroporphyrinogen decarboxylase	Sporadic (80%) AD (20%)	1: 25,000	Photosensitivity (bullous)
Hereditary coproporphyria (HCP)	Coproporphyrinogen oxidase	AD	<1:250 000	Acute attacks and/or bullous photosensitivity
Variegate porphyria (VP)	Protoporphyrinogen oxidase	AD	1:250 000	Acute attacks and/or bullous photosensitivity
Erythropoietic protoporphyria (EPP)	Ferrochelatase	AD	1:100 000	Photosensitivity (acute)

* Refers to symptomatic cases.

Porphyria services

This is a description of the current clinical and laboratory services available for patients with porphyria. As mentioned, many patients with porphyria are managed by clinicians with little or no experience of these disorders. In addition most hospitals with acute medical services screen for acute porphyria by measuring urine porphobilinogen and total porphyrin. Positive findings are usually referred to a more specialised laboratory for confirmation and full porphyrin analysis. A major role of specialist laboratories is also to exclude the diagnosis of porphyria as a cause of clinical problems. There are well-recognised examples of patients in whom an erroneous diagnosis of porphyria has been made, leading to many years of inappropriate and costly treatment.

There are two levels of specialised clinical biochemistry services.

1 Regional units

Regional units have an interest in porphyrin biochemistry and offer a range of biochemical tests, including urine, faecal and blood porphyrin analysis and interpretation of results. This requires dedicated instruments such as a fluorimeter and an HPLC (high performance liquid chromatography) system with a fluorescence detector. There may also be a chemical pathologist and/or clinical scientists with a particular interest in porphyria providing limited clinical services. Examples of regional units include services in Bedford, Belfast, Dundee, Leeds and Salford.

2 Supraregional Assay Service laboratories

The Cardiff and London KCH porphyria services are both recognised by the Supraregional Assay Service (SAS) organisation (www.sas-centre.org/) as centres offering expert analysis, clinical interpretation and consultative clinical back-up. Each service has a director and deputy director responsible for delivery of the service as well as service developments. They also provide the following services (workload data in Table 6.2):

1. Out-patient clinical services
2. In-patient services in collaboration with a local physician
3. Clinical advice to patients and clinicians (letters, email, telephone)
4. Advice to other clinical biochemistry departments on investigation of patients, training and education of clinical scientists
5. Clinical and technical advisory support to the regional units
6. Undertake research in the field.

Both are members of the European Porphyria Network (www.porphyria-europe.org). Staff from Cardiff have been involved in setting up this group and developing the consensus information published on the website.

In addition to these services, the Cardiff Porphyria Service provides the following:

1. Genetic testing for all porphyrias (apart from ADP) which is recognised by the UK Genetic Testing Network.
2. A drug safety advisory service in collaboration with the Welsh Medicines Information Centre (WMIC). The service provides a safe drug list that is updated annually and staffs a telephone helpline during office hours. The annual workload (August 2004 – July 2005) amounted to 532 drug enquiries.
3. Equivalent to one WTE experienced medicines information pharmacist.

Table 6.2 Workload data for SAS services

Porphyria services	Cardiff	London KCH
Laboratory referrals (per annum)	2,374 (5,846 tests)	750 (1,500 samples)
New diagnoses (per annum)	189	33
Staffing		
Consultant:	0.6 WTE	0.1 WTE
Principal biochemist	0.5 WTE	0.9 WTE
Biomedical scientist 2	1.5 WTE	1.0 WTE
Biomedical scientist 1	2 WTE	
Clinical: out-patients	Adult metabolic clinic (monthly) Dermatology porphyria (bimonthly)	Porphyria clinic (monthly)
	30 patients per annum	70 patients per annum
	15–20 new referrals per annum	21 new referrals per annum

Clinical-only services

There are at least three clinical medicine departments with a particular interest in porphyria, primarily acute porphyria. These services are in Cambridge, Birmingham (Liver and Hepatobiliary Unit) and Glasgow. A formal audit would be required to provide information about the number and range of patients being managed by these units.

Two photobiology units have a special interest in porphyria: St John's Institute of Dermatology in London and the Dermatology Department in Dundee.

Networking

The Porphyrin Interest Group – comprising clinicians, laboratory scientists and representatives of the British Porphyria Association – meets annually. This meeting is sponsored by the pharmaceutical industry.

Funding

The SAS porphyria services are funded via a fee-for-service system, mainly for laboratory services, and where relevant clinical referrals. Other aspects such as the clinical advisory service, drug safety service and other organisational and networking responsibilities are unfunded. There is no funding to support recruitment and training of clinical or laboratory staff.

Conclusions

1. The porphyrias are a group of rare metabolic diseases, most of which present in adulthood, for which clinical and laboratory services are not formally organised and are therefore vulnerable. In view of this ad hoc service, there are no formal data on the number of patients who require clinical support. Many patients diagnosed with porphyria are not referred to a clinician with a special interest in the porphyrias unless problems arise.
2. Patients with very severe porphyria, or serious complications such as recurrent attacks or rare types of porphyria (e.g. CEP), should be referred to one or two clinical centres with the appropriate facilities that can develop the experience and expertise to deal with these complex clinical cases.
3. A network of clinical and laboratory services is required to support optimum clinical care for patients with porphyria. This should include:
   - access to specialist clinical services for all porphyria patients
   - support and advice for non-specialist clinicians
   - support for the UK drugs advisory service
   - support for recruitment and training of successors.

7 Nursing services

1 Introduction

An experienced nurse plays an important role in the multi-disciplinary team for IMDs. The work is highly specialised and involves complex aspects of care for individual patients, as well as working on familial aspects of disease with the extended family. In addition to direct clinical work with families, specialist nurses take on roles within the organisation such as leading clinics, providing first-line telephone information and advice, undertaking teaching, coordinating services, researching and becoming involved in commissioning.

A review of the nursing role and current service input was undertaken as part of a larger needs assessment and review of IMD services in the UK in 2005. Information was gained from a survey of main centres providing specialist services, a survey of specialist nurses in the nurse network of the British IMD Group, and a focus group of nine specialist nurses from centres around the country.

2 Review of the specialist nursing workforce within the UK

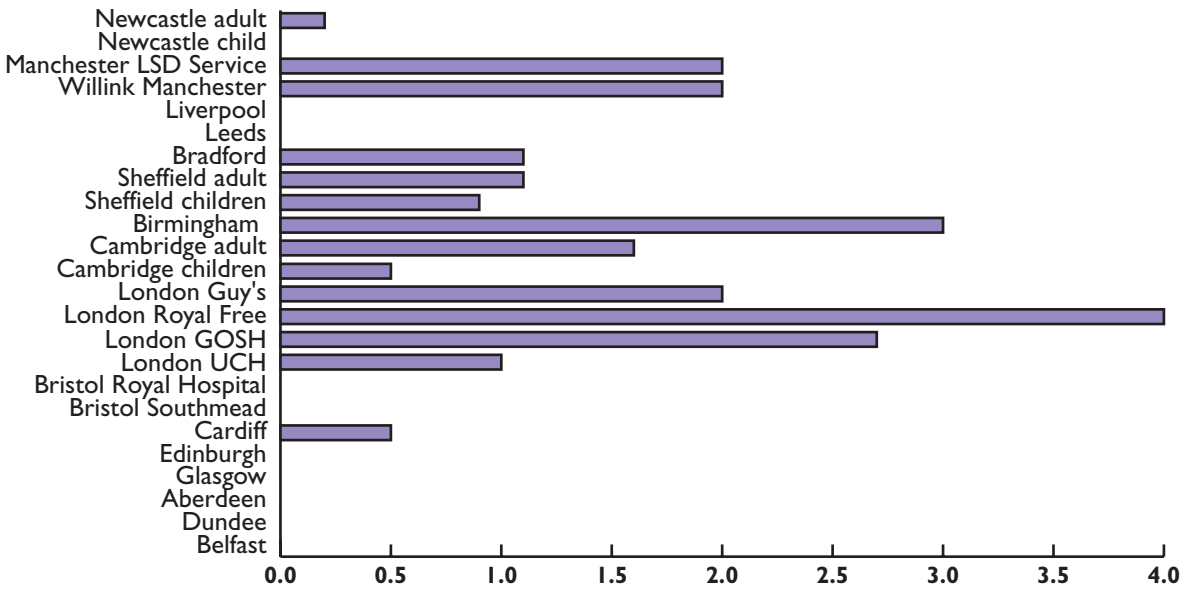
2.1 Overview

The main survey revealed a total of 29 nurses working in specialist IMDs, based in 14 centres across the UK. Ten metabolic service providers did not have a nurse specialist; these included all of the services in Scotland and Northern Ireland. In a further four centres the nurse specialist was single handed. The total number of WTE devoted to the specialist IMD services was 22.6, representing 78 per cent of potentially available nursing time.

Through the BIMDG nurses group, a questionnaire was sent to 23 nurses working in the field of IMDs. Fourteen replies were received (61%).

Figure 7.1 gives a summary of the nursing workforce in the various services across the UK.

Figure 7.1 Nurses working in specialist IMD services (WTE)



2.2 *Job titles*

There appears to be a range of job titles for nurses working in the various services providing care for those affected with IHDs. The most common title was Clinical Nurse Specialist.
Others include:

- Clinical Research Nurse
- Liaison Sister
- Metabolic Research Nurse
- Nurse Specialist
- Practice Educator
- Sister.

The age ranges of respondents was 25–34 (25%), 35–44 (42%) and 45–54 (33%).

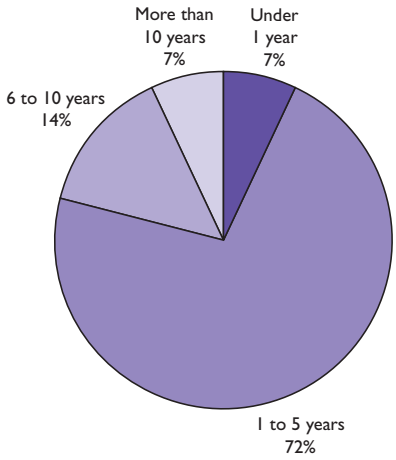
2.3 *Professional qualifications, training and experience in inherited metabolic disorders*

Nearly all respondents indicated that their professional qualifications included RGN or RN, and two thirds had a primary degree. Three of the respondents (20%) had or were in the process of getting a higher degree.

The formal training reported included study days, conferences and training on the job.

The duration in the current posts of respondents is shown in Figure 7.1. Almost 75 per cent had been in post for one to five years, 21 per cent more than six years, and 7 per cent less than one year.

Figure 7.2 Duration in current specialist post



The pathway to the present post of respondents was varied. The commonest route was from a general nursing post involving some experience of the care of those with IMDs.

3 Specialist nursing roles in inherited metabolic diseases

Following a discussion of special expertise in clinical cases with a group of nine nurse specialists in IMDs, clinical specialist roles were agreed to include:

- providing specialist information, practical and emotional support to patient and family in acute phase of illness and over long periods

- providing specialist expertise to other clinical teams
- managing acute crises
- multi-disciplinary work
- managing familial aspects of disease, including dealing with potential dilemmas of family screening
- managing clinical trials expectations
- managing misdiagnosis from other services.

These are illustrated in accompanying case histories.

Other general roles include:

- education
- coordination
- telephone advice
- providing a nurse-led service
- setting up, monitoring and tendering for homecare systems
- administrative responsibilities in relation to NSCAG.

3.1 Case histories to support specialist clinical and other roles

The following eight case histories illustrate the specialist nursing roles in IMDs in the context of clinical care.

(a) Supporting parents with an acute presentation in a newborn baby

Judith was a newborn baby girl to parents of a consanguineous marriage. They previously had a male child who died as a neonate and the brother of one and sister of the other (who married each other) had a male infant who had died just two weeks previously. The nurse specialist was asked to see the mother in the maternity unit. The baby at this time was in the intensive care unit undergoing ventilation and haemodialysis with a diagnosis of OCT deficiency.

Her main role at first was to help the mother and family understand the condition by explaining it in simple terms. They also needed to start to understand the familial aspects and come to terms with the perceived guilt of having passed on a genetic condition.

As Judith got through the acute phase of the illness, the nurse became involved in many arrangements for the transfer home, liaising and providing education for community staff and local dietitians and arranging post-discharge follow-up. She made frequent home visits and provided support through several admissions for metabolic decompensation when Judith became ill again.

(b) Providing specialist information, practical and emotional support to patient and family over long periods

Richard was a 45-year-old man with Fabry disease. He was referred to the specialist unit, having been diagnosed the previous year with Fabry disease when he was seeing the cardiologists for left ventricular hypertrophy.

Richard attended the specialist clinic with his wife and was seen first by the clinical nurse specialist, who gave them some information about Fabry disease. The nurse also told them about some of the other investigations that would be recommended, and allowed the family plenty of time to ask questions prior to their appointment with the consultant. The nurse went on to organise the necessary investigations. It was found that his renal function was relatively poor.

Richard fitted the criteria for ERT and the nurse saw him on a fortnightly basis to administer this.

During the subsequent year, Richard's renal function deteriorated, causing both him and his family a great deal of concern. The nurse spent a lot of time on the telephone with them, trying to respond to their anxieties. The family had felt that by his starting ERT, his renal function would be preserved. It was reiterated that whilst ERT might slow the progression to chronic renal failure, Richard's kidneys were quite damaged by the time ERT was started.

Eventually, his renal function reached the point where he required peritoneal dialysis, and he was also put on a waiting list for renal transplant. At this stage the nurses provided support to their colleagues on the renal unit, giving information about Fabry disease, and in particular guidance on such aspects of management as ERT. The importance of continuing with ERT was also emphasised to the family as this would help protect Richard's heart and brain from further damage due to Fabry disease.

(c) Managing an acute crisis

Derek, aged 38, was a patient with Gaucher disease who attended a national specialist centre for treatment and monitoring. He was admitted to his own local hospital with severe back pain, numbness in the left leg and evening pyrexia. With his consent, his wife contacted the specialist nurse at the centre and, as there was a shared care protocol in place between the centre and the local hospital, the specialist nurse was able to become directly involved in his care. She was able to give advice straightaway on pain management, advising the local staff to refer to the pain management team to provide an effective regime. She was also able to advise medical staff on the appropriate investigations, and results were then evaluated by both local and centre staff. Differential diagnosis was important to exclude the possibility that Derek might have serious spinal complications. This was subsequently ruled out following X-ray and MRI scanning, which was reviewed by the specialist centre. During this time the clinical nurse specialist made a number of visits to the local hospital, provided much information and emotional support to the patient and family – whom she knew well – and teaching and training to the ward staff to help them to manage this case effectively.

(d) Multi-disciplinary work to manage the angry adolescent

Mary was a 17-year-old symptomatic patient with Fabry disease and exhibiting low enzyme levels. She had a family history of the disease, in that her father was quite severely affected and died aged 46 having had several strokes and having developed renal failure requiring kidney dialysis and experienced a failed kidney transplant. No mutation was found. She had a sister and two nephews affected with the disease.

Mary was recently recruited to an ERT trial and was determined to 'find help' for her nephews. However, she was still grieving for her father, who had died only 12 months previously, and was going through quite a traumatic grieving process, exhibiting anger, denial, heartbreak, disbelief, self-abuse with alcohol and drugs and being sexually promiscuous. Surprisingly, she was very compliant with those providing care within the trial – having skin, kidney and cardiac biopsies – but very irrational and badly behaved outside this. To the nurse she admitted to drinking a bottle of vodka a day and smoking cannabis.

Just before the second renal biopsy, she told the nurse that she wished to kill herself as she could not deal with the death of her father and the extreme pains in her hands and feet that she suffered as a result of the disease.

The nurse recognised this as a crisis, and in responding enlisted the help of the mental health crisis team, ongoing counselling, and the drug and alcohol rehabilitation unit – as well as working with the IMD physician, Mary's parents and Mary herself. This illustrates the multi-disciplinary approach to patient management instigated by the specialist nurse, including liaison with various other disciplines for variable time periods.

To the uninformed, Mary looked well. The special relationship with the nurse enabled this crisis to be managed safely with a positive outcome and ongoing care.

(e) Managing familial aspects of the condition

John was a 43-year-old, apparently healthy, man who was diagnosed with Fabry disease following a routine medical in association with new employment. The discovery of proteinuria led to referral to a renal physician, and a scan of the kidneys showed shrunken bilateral kidneys. Further investigation led to a diagnosis of Fabry disease and it was found that he also had cardiac involvement. A genetic analysis identified a gene mutation. There was no known family history.

John was referred to a specialist centre, where it was decided that family members at risk should be traced and testing offered. The nurse specialist made contact initially with John and began to construct a family tree. John's mother had died of renal failure; this was now thought to be Fabry disease. John had three sisters who were counselled and all were screened. All three sisters were found to be gene carriers and two, although asymptomatic, had some renal damage.

While screening the family members considered at genetic risk, John informed the centre of his nephew, Stephen, presenting at his local DGH with a stroke at 41 years. The nurse specialist visited Stephen at the DGH. He had presented with a right-sided hemiplegia, no speech, and post-stroke seizures. The family had no knowledge of the existing diagnosis in the uncle's case. On further exploration of Stephen's medical history, signs and symptoms of Fabry disease were found to have been present in childhood. He had felt pain in his hands and feet as a boy, and was found to have angiokeratomas (benign vascular skin lesions characteristic of Fabry disease). Stephen was invited to the centre, and following an assessment commenced on ERT.

Stephen and his wife had four children. Two of the daughters confirmed that the eldest daughter was adopted at birth and they had no contact with her. They now realised that she would have inherited the Fabry gene and they wanted her to have this information. The nurse specialist ensured that information was forwarded to the adoption agency. They contacted the girl, resulting in her referral to the specialist centre.

(f) Dealing with potential dilemmas in family screening

Susan, aged 29, with three young children aged 12, 8 and 4, using an internet website Genes Reunited discovers her half-sister and makes contact. She had been brought up in a care home and this is her first contact with blood relatives.

The newly found sister informs her relations that there is an IMD in the family – Anderson-Fabry disease. She puts her half-sister in contact with a specialist centre where she can receive counselling and advice. Using the internet, she has already gained some lay-person knowledge of the condition, but some of it is misleading and frightening. The team at the specialist centre is able to give helpful and reassuring advice and education that enables the mother to make a choice about screening her children and herself.

Genetic screening for Anderson-Fabry disease is undertaken, and the results show that the mother, her two sons and daughter test positive for the family DNA mutation. Further testing of cardiac and renal function enables them to make informed choices about treatment.

With legislation that enables adopted children to seek out their parentage and the prevalence of electronic means of doing this, such situations will become more commonplace. The role of the metabolic team is to prevent these dilemmas from becoming a family crisis.

(g) Managing misdiagnosis

This case history highlights the problems of non-specialist centres giving information without up-

to-date information, and the importance of parents having access to someone who is really knowledgeable about a condition at the time of diagnosis and during management, and who has networks to provide parent support.

Indira was a newborn baby girl who presented with severe neonatal jaundice and organomegaly. Initially it was thought that she had a severe infection and she was treated with antibiotics. However, there was no resolution and the liver disease persisted over the next few weeks, when it was thought that she had biliary atresia. Her parents were told that the liver disease was so severe she would die. A scan, followed by surgery, showed that this was not the case, and over the next six months she had further four liver biopsies Eventually storage cells were found in the biopsies and a full metabolic work-up was performed, which eventually showed that she had Niemann Pick disease.

At this point, the parents were informed that Indira would not develop normally, would never walk or talk, and would die before the age of 2 years. By the time she was referred to the specialist team, the parents had already been referred to the local palliative care team.

The first task for the specialist nurse was to pick up the pieces as the parents were in despair. She was able to tell the parents that the natural history of the disease was variable, and they were introduced in the clinic to parents of children up to the age of 5 who had no neurological problems, so that they could see that the outlook was not as bad as they had originally been told. They were also told that there would be a possibility of genetic counselling for them, and that there might be other options for them if they wished to have more children.

When Indira was seen in clinic, at age 9 months, she was still very jaundiced. However, the last report on her at age 17 months was that she was developing well, had learned to walk and was speaking about 18 recognisable words.

(h) Managing clinical trials expectations

Neuropathic Gaucher disease is a life-limiting illness with very poor genotype-phenotype correlation. ERT has changed the prognosis of this disease, maintaining children's visceral disease relatively well. Family fears of neurological deterioration and premature death are high.

Clinical trials exploring a smaller molecule to halt neurological progression started in July 2003. Parental expectations were extremely high. This was seen as the new 'cure'. The delay in commencement of the trial led to anxiety, anger and frustration.

Managing parental expectations in a realistic way is very problematic. Parents hear what they want to hear. They cling on to the information they want. The research nurse must maintain a realistic view of the issue. The risk of their child 'failing' screening prior to admission to the trial due to poor cooperation, and especially level of disease progression, adds significant tension and stress. When one sibling 'succeeds' in screening and starts treatment while the other sibling fails (often being the more severely affected sibling as well), this opens up an array of emotions that are very difficult to support and manage. Randomising siblings (even if the trial is blinded) causes similar emotions and situations.

The research nurse managing the trial must also inform and educate other professionals and departments about the impact and implications of the trial, and treatment on clinical management and resources and so on, and future prediction of services.

Metabolic treatments being developed and introduced into clinical care are an increasing aspect of our workload. As well as understanding the disease itself and the various treatments, the nurse needs to be fully conversant with ethical considerations in clinical trials, research governance, liaising with other professionals, working with the pharmaceutical sponsor, and the reporting and presentation of results.

3.2 Organisational roles undertaken by the clinical nurse specialist

Education

Specialist nurses in IMDs have a key role in the provision of education of health professionals. This is undertaken in the context of care for the individual patient and more widely, including nursing students and any other allied health professionals, medical students, general practitioners and those training and undergoing CPD in paediatrics.

One further large element of education has arisen recently, in which nurses are involved in supporting the neonatal screening programmes and will be particularly involved in the roll-out of the MCADD programme with teaching required for midwives, health visitors, community paediatricians and local hospital paediatricians. This has been implemented on the whole by specialist nurses for IMDs.

Providing telephone advice

The specialist nurse is often the first port of call for GPs or geneticists who have a patient that they suspect or know has an IMD. The nurse will usually give information on the disorder, how to refer and what other tests to do to confirm the diagnosis.

Nurses are also called by patients who have seen, read or researched a disorder and believe they might be at risk. The nurse will provide information about the disorder, and tell them if it sounds likely and how to get referral.

Coordination

Patients and families with severe chronic disease need a key worker to link the multi-disciplinary team and the wider group of health and other professionals and voluntary organisations concerned with the care of the family. The clinical nurse specialist often fulfils this role. She may initiate and then subsequently attend a multi-disciplinary team meeting. As the family's needs increase, she may introduce other specialists and she may have a particular role here in coordinating appointments for the family who have long distances to travel.

Provision of a nurse-led service to provide patient care

This role is not yet officially recognised, but does occur in the IMD service. Experience of those undertaking such a service, notably at the Manchester Fabry Centre, is that this is very positive and a good way of dealing with diagnosis and future care monitoring.

Setting up, and monitoring and also tendering for homecare systems

Department of Health regulated, but privately run, homecare companies are often used in IMDs – for example in the administration of ERT infusions at home. It is increasingly the clinical nurse specialist's role to be involved in commissioning and tendering for these services. Once set up, these systems need to be monitored continuously for quality by the nurse, using information gained from patient audit. The metabolic nurses are the first point of call for homecare nurses for crisis management.

Administrative responsibilities in connection with NSCAG

The CNS role with NSCAG includes administrative responsibilities such as providing activity data, quality reports and ERT financial monitoring. This also includes future service planning.

4 Education and professional development for specialist nurses

4.1 Education and training reported by UK nurses from survey

Respondents to the nursing survey commented on the present state of training for nurses and what could be improved. The main point was that there is no formal nurse training in IMDs. Most practitioners have simply learned on the job, sometimes with an initial bit of training as part of their induction. They then go on to have further training through ward rounds and attendance at various educational meetings. Some support to nurse education is provided through the nurses' network of the BIMDG.

Educational needs

Formal and accredited education for nurses in IMDs is urgently needed, and should be at basic level as an introduction and at a more specialist level. It should cover clinical aspects, pathophysiology, genetics, biochemistry, dietetics, social and psychological aspects, research and development aspects, as well as the nursing role in providing support for patient and family.

As a preliminary to this, key competencies should be set out on a national basis and courses should be recognised and accredited.

As an adjunct, professional development for nurses should be supported through grants to enable attendance at national and international meetings, seminars and workshops. One example is that the annual Gaucher course at the Royal Free Hospital in London, currently offered to physicians from other countries, could be offered to nurses from Europe too.

5 Recommendations

Development of the specialist nursing role

1. The role of the nurse in the IMD team is highly specialist and integral to the service. There should be clinical nurse specialist posts in every major centre.

2. There are opportunities for clinical nurse specialists to take on substantial areas of the service. However, their extensive roles need to be properly recognised and adequate resources in terms of session time and support made available for them to be undertaken properly. This would allow services to:

   - provide high-quality nursing care
   - develop the wider health services to be able to provide competent care and thus support the role of the specialist service
   - care for more patients by freeing consultant medical time through the provision of nurse-led clinics and services
   - develop good networks of specialist care between centres and districts with shared care protocols.

Education

1. Education should be developed further and formalised as follows:

   - There should be development of a formal course at Master's level, which should cover clinical aspects, pathophysiology, genetics, biochemistry, dietetics, social and

psychological aspects, and research and development aspects, as well as the nursing role in providing support for patient and family.

- There should be an agreed formal training programme that includes theoretical, practical and professional aspects of the work. This should be developed to include documentation of education by the trainee.
- Clinical nurse specialist posts in this area need to be created so that those in training can have an expectation of a post being available.
- Clinical nurse specialists in training and others already in post must be supported to undertake more formal education – recognising that this is highly specialised and cannot be undertaken simply within the home service.
- There should be more formal training rotations that take in a period of training at one of the main specialist centres. These centres should be formally recompensed for the time they spend teaching.
- Each region / specialist centre should have a clinical nurse specialist with a lead role for education in IMD.
- Clinical nurse specialists must have the necessary time and resources to undertake teaching.

8 Dietitian services

1 Introduction

An experienced dietitian plays an important role in the multi-disciplinary core team for inherited metabolic diseases (IMDs). The work is highly specialised and complex. Good dietary management is crucial to the outcome in many of these conditions.

The specialist dietitian leads and is responsible for the individualised dietary management of children and adults with IMD. This involves formulating the diet and teaching patients, parents, carers and other relevant lay persons about the patient's dietary treatment. The dietitian provides support and collaborates with smaller specialist units and district general hospitals, providing expert advice and education to medical, nursing and allied health professionals. In addition, the dietitian will provide advice and support on the dietary management of patients with IMDs to other professionals in health, social care and education. Dietitians are also involved in research, development of protocols and education.

A review of the dietitian's roles and current service input was undertaken as part of a larger needs assessment and review of IMD services in the UK in 2005. Information was gained by: a survey of main centres providing specialist services; a survey of dietitians through the BIMDG dietitians subgroup; and a focus group of three dietitians from centres in London and Manchester.

2 Review of the dietitian workforce in IMD services in the UK

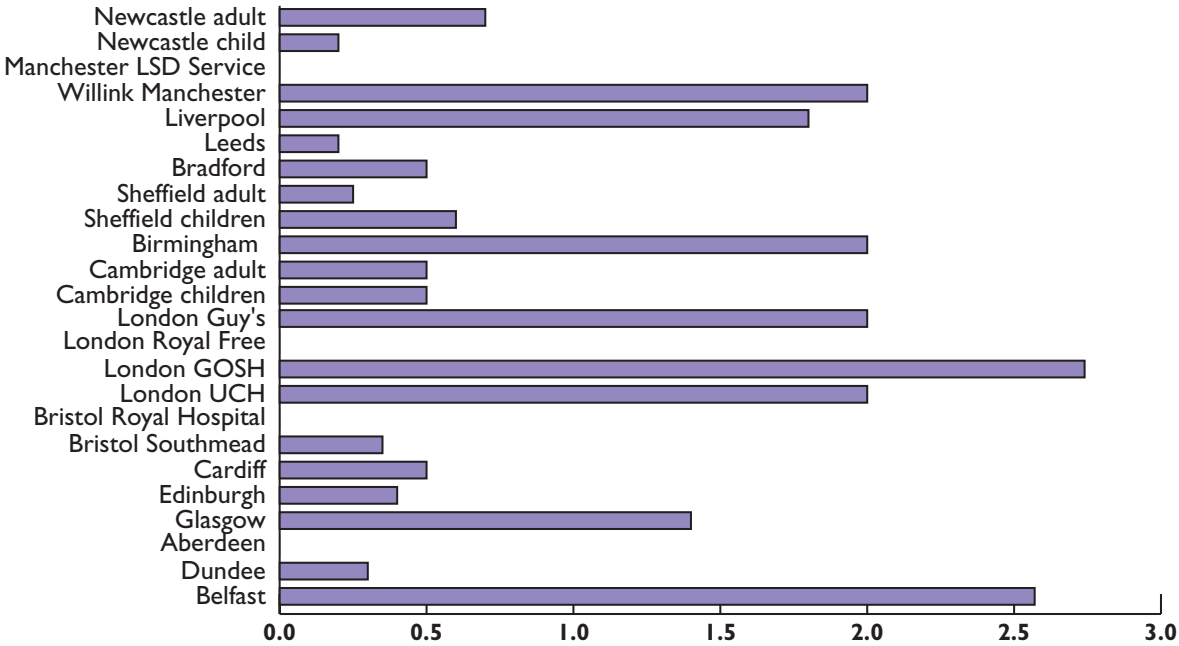
2.1 Numbers and distribution

Services were asked to provide information on the number of dietitians involved in the provision of specialist IMD services, including details on whole time equivalents (WTEs) devoted to IMD work. This included information from 24 service providers. In addition, questionnaires were sent to 27 dietitians identified through the BIMDG dietitians subgroup, asking for further information about areas of work undertaken, education, training and experience, and perceptions of unmet need and service shortfall. Seventeen replies were received. The results are shown in Figure 8.1.

A total of 35 dietitians working across the UK were identified by service providers, between them contributing 22 WTE. This accounted for 63 per cent of the potential WTE available if all were full-time on IMDs. In two centres providing core IMD services there was no dietitian, and in a further nine the dietitian was single handed. In only nine services was there more than one WTE dietitian.

It needs to be recognised that at Manchester and London GOSH 0.75 WTE and 1.0 WTE (2 individuals) respectively are training posts, not specialist posts.
In Newcastle one dietitian is split between child and adult services.
There are dietitians from other services managing IMD patients who work and liaise quite closely with the main centres – for example, in the context of outreach clinics. These dietitians might not have been included in the study.

Figure 8.1 Dietitian workforce in the UK



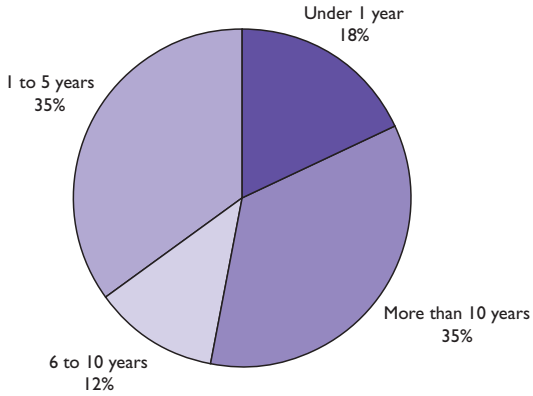
A survey of dietetic workload was undertaken by the BIMDG dietitians group in 2004. The ratio of specialist dietitian to number of patients is given below. It can be seen that this varies from 1:115 in Glasgow to 1:460 in Manchester. (Note that this ratio again includes training posts).

Service	Patients/wte
Manchester	460:1
Liverpool	438:1
Birmingham	366:1
London Guys	120:1
London GOSH	227:1
London UCH	265:1
Glasgow	115:1
Belfast	136:1

2.2 *Age range*

Dietitians' age ranges were 25–34 (20%), 35–44 (33%), 45–54 (40%) and 55+ (7%). Respondents were asked about duration in their current post. Almost 20 per cent have been in post for less than one year and fewer than 50 per cent have been in post for more than five years (see Figure 8.2).

Figure 8.2 Duration in current specialist post



3 Roles of specialist metabolic dietitians

3.1 Clinical roles

The clinical roles include the following:

- Formulation and calculation of IMD feeding regimens for patients when they are well or unwell.
- Prescribing specialised metabolic dietary products to be used in treatments.
- Intensive monitoring (biochemical, growth and tolerance) of response to dietary treatment with necessary dietary adjustment.
- Long-term follow-up and assessment, adjusting dietary regimen according to growth, biochemical findings and clinical progress.
- Assessment, monitoring and adjustment of dietary regimens during pregnancy.
- Education for patients, their families and carers using a range of communication skills.
- Providing counselling and emotional support to patients, their families and carers on the practical implementation and management of highly complex dietary regimens.
- Key worker, particularly for patients where diet is the sole or major treatment; thus, providing a link between the family, the multi-disciplinary team and community professionals.
- Education, support and liaison with health professionals and others involved in the care of the patient (including professionals from education and social services), both in the specialist centre and in the local community.
- Referral to other professionals as appropriate, such as to speech and language therapy, clinical psychology (e.g. for help in management of adverse feeding behaviour), feeding and swallowing problems, psychological support for managing dietary treatment.

3.2 Provision of therapeutic dietary treatment

Dietary therapy is the mainstay of clinical management in three main groups of IMD: disorders of protein metabolism (amino acid disorders, organic acidaemias, urea cycle disorders), disorders of carbohydrate metabolism, and disorders of lipid metabolism (see Figure 8.3).

Figure 8.3 Inherited metabolic diseases requiring therapeutic dietary management box for lists of main disorders).

A Protein

Amino acid disorders

- PKU
- MSUD*
- Tyrosinaemia
- Homocystinuria
- Hyperornithinaemia
- (gyrate atrophy of the choroid & retina)

Organic acidaemias*

- Propionic acidaemia
- Methylmalonic acidaemia
- Isovaleric acidaemia
- Glutaric aciduria type I

Urea cycle disorders*

- OTC deficiency
- CPS deficiency
- Citrullinaemia
- Argininoosuccinic aciduria
- Arginase deficiency

B Disorders of carbohydrate metabolism

- Galactosaemia
- Hereditary fructose intolerance
- Fructose 1, 6 bisphosphatase deficiency*
- Glycogen storage diseases* mainly types I, III, IX

C Disorders of lipid metabolism

- Type I hyperlipidae mia
- Familial hypercholesterolaemia
- Fatty acid oxidation disorders*
  - VLCAD
  - LCHAD
  - MCADD
  - Carnitine transport disorders
- Peroxisomal disorders
  - Refsums disease
  - Infantile Refsums
  - Adrenoleukodystrophy

* denotes disorders requiring emergency dietary regimen during illness

Example 1 Management of an amino acid disorder: phenylketonuria (PKU)

PKU is due to a deficiency of the enzyme phenylalanine hydroxylase. This results in the accumulation in plasma of the essential amino acid phenylanine (phe) which is neurotoxic. Without dietary treatment this accumulation would cause severe learning difficulties. Phenylalanine is normally converted to tyrosine, so tyrosine becomes deficient. To prevent phe toxicity, the diet needs to be restricted in phe intake. Tyrosine is supplemented to ensure adequate intake to prevent deficiency of the essential products of tyrosine degradation. Dietary treatment continues throughout childhood. Some adults remain on the diet, and diet is essential during during pre-conception and pregnancy to prevent damage to the baby, such as microcephaly and congenital malformations.

The dietitian will formulate, manage and continuously monitor a low-phe diet to support normal growth and development as follows:

1. Restrict natural protein intake to maintain plasma phe level within desirable reference range for age
2. Prescribe phe-free amino acid supplements to achieve an adequate protein intake
3. Ensure adequate intake of tyrosine and prescribe tyrosine supplements in maternal PKU
4. Prescribe vitamin and mineral supplements

5. Maintain normal energy intake using special low-protein prescribable foods
6. Manage the diet based on plasma phe results.

Example 2 Management of a disorder of carbohydrate metabolism – galactosaemia

Patients with classic galactosaemia are unable to catabolise dietary galactose (milk sugar) owing to a deficiency of the enzyme galactose-1-phosphate uridyl transferase. The presenting clinical symptoms seen in infancy – such as jaundice, hepatomegaly, liver failure and cataracts – will resolve with dietary treatment of strict avoidance of dietary galactose. The dietitian will advise on the exclusion of dietary galactose and monitor the diet to ensure an adequate intake of all nutrients, especially calcium. Dietary treatment needs to be lifelong.

3.3 Emergency dietary regimens

For some inborn errors of intermediary metabolism, intercurrent illness combined with a poor oral intake and fasting will cause severe metabolic decompensation. Such children may rapidly become extremely ill, sometimes encephalopathic, and require admission to intensive care units. To prevent this, an emergency diet is given which varies depending upon the disorder. The dietitian is instrumental in the provision of this, either at home by frequent telephone contact or in hospital.

3.4 Nutritional support

Patients with other IMDs – including mitochondrial disorders, LSDs and some peroxisomal disorders – do not require specific therapeutic dietary management as a primary treatment. However, individuals with these disorders may have more general nutritional problems, including swallowing problems which require dietetic intervention to provide nutritional support.

3.5 Case histories

Two case histories illustrate the intense and specialist clinical role of the IMD dietitian.

Case history (a) The acutely ill child with an amino acid disorder

Rajesh was born to first-cousin Asian parents. At 11 days old he became very unwell, with very poor feeding and lethargy, and was admitted to his local district general hospital. He had poor muscle tone and was encephalopathic. Initial investigations revealed raised plasma branch chain amino acids (BCAAs)and a diagnosis of Maple Syrup Urine disease (MSUD) was made.

He was transferred to the ICU at the tertiary metabolic unit, where he was ventilated and commenced on dialysis to reduce the plasma leucine level (leucine is neurotoxic at high levels). The mainstay of treatment for MSUD is diet (limiting intake of BCAAs). Dietary treatment was begun immediately on Rajesh's arrival in ICU. A modular feed free of BCAAs was given. This feed had to contain sufficient BCAA-free amino acids and energy to promote the conversion of leucine to body protein, thereby reducing plasma leucine level.. He was fed via a nasogastric tube.

Over the next few days, the dietitian reviewed his feeds daily. These were adjusted according to the plasma BCAA levels, weight, fluid allowance and feed tolerance. Branch chain amino acids were monitored daily during the acute phase.

BCAAs are essential amino acids. Once the high plasma leucine level had decreased, a measured amount of natural protein as infant formula was added to the modular feed to provide a source of BCAA.. The amount of infant formula was altered to maintain plasma leucine levels within safe limits. Due to low levels of the other two BCAAs, valine and isoleucine, supplements of these were given to prevent them from being rate limiting for protein synthesis. The amounts prescribed were altered according to plasma levels.

The dietitian worked closely with the ICU nurses and intensivists as they had a very limited knowledge of MSUD and did not fully understand the importance of dietary management to the outcome. There was also close liaison with other members of the metabolic team (medical, nursing, biochemists), pharmacy and the special feeds unit.

After a few days Rajesh was well enough to be transferred to the ward, where he was gradually moved from nasogastric to oral feeds. During the next two weeks he was stabilised onto a feeding regimen which included a measured amount of normal infant formula, a BCAA-free formula, valine, isoleucine and calorie supplements.. An emergency regimen would also be required for use during periods of intercurrent illness.

During this initial admission, one of the important roles for the dietitian was education of the family. This was complicated by the fact that the mother had limited English and any teaching about diet had to be undertaken in the context of an Indian family diet. The dietitian undertook teaching in several stages, using an interpreter, and always reinforcing verbal information with written information. The family needed to understand:

- *the principles of dietary management*
- *what an MSUD diet consists of*
- *how to make up the special feeds very accurately*
- *how and when to put in place the emergency regimen for Rajesh if he should become ill.*
- *what products can and should be used in the diet and how to avoid the risk of using the wrong products*
- *the importance of monitoring plasma BCAA levels and how the dietitian interprets these and makes dietary changes.*

Sometimes teaching was in several sessions daily and included the extended family.

Before discharge, the dietitian made contact with health professionals who would be involved in caring for Rajesh when he returned home into his local community area, to explain his dietary treatment when well and unwell. This included consultant, local dietetic services, local pharmacy, health visitor and GP.

Rajesh was discharged home at 5 weeks of age.

After discharge he continued to have weekly blood tests to monitor BCAA. The results were interpreted by the dietitian, who phoned the family every week to discuss progress, weight, blood results and any necessary feed changes. A further period of intensive dietetic advice and support was needed at the time of weaning. The dietitian was also called by the family for advice when Rajesh was unwell, and discussed whether to institute the emergency regimen, when to contact the doctor or bring him to the hospital. She was also involved in giving advice regarding other medication and immunisations. Support to the family for Rajesh was also provided by involvement in community meetings to discuss what his dietary requirements in nursery and school were.

Case history (b) Management of maternal PKU

Barbara has phenylketonuria (PKU), which was diagnosed on routine neonatal screening. She was started on a phenylalanine-restricted diet at 2 weeks of age which was relaxed at 8 years of age and then further in her teenage year, but she still had great problems in adhering to the diet. When she was 27 she was allowed to come off the restricted diet completely and eat an unrestricted diet including high-protein foods.

At the age of 30 Barbara attended a clinic appointment with her partner to discuss that they were getting married in a few months and would like to plan a pregnancy straight away. The doctor and dietitian both confirmed the importance of Barbara going back onto a phenylalanine-restricted diet before she became pregnant and to continue this throughout pregnancy, to ensure that her unborn baby would not harmed by

high phenylalanine levels. They explained what would be involved in terms of re-education of the diet for pre-conception and during pregnancy, the frequency of blood tests, and the frequency of clinic appointments.

A date for re-education was set. Barbara attended the clinic and saw the dietitian and dietetic assistant (DA), who is involved in the practical dietary teaching/cooking with the patient. In total she attended for four days of intensive dietary re-education, and her husband attended the first day to learn more about PKU and what is involved with diet for pregnancy.

During the four days of re-education the following were covered by members of the multi-disciplinary team (individualised to Barbara's needs) and coordinated by the dietitian:

- *amino acid supplement tasting (RD)*
- *explanation of diet with written diet sheets (RD)*
- *tasting low-protein prescription products (DA)*
- *learning to do a finger prick test and send in a blood spot card (CNS)*
- *following recipes using low-protein prescription products (DA)*
- *calculating and weighing protein (phenylalanine) exchanges (DA and RD)*
- *supermarket visit (DA)*
- *planning meals and menus using a certain number of protein (phenylalanine) exchanges (DA).*

DA = metabolic dietetic assistant, supervised by the dietitian
RD = metabolic dietitian
CNS = metabolic nurse specialist

The pre-conception dietary management aims for phenylalanine levels of 100–250mmol/L. During this time Barbara had twice weekly finger prick phenylalanine blood tests. Blood results were reported by telephone and any changes to the diet discussed. Barbara became pregnant in April 2004. During pregnancy she had more frequent blood tests, three times a week. The diet became more complicated as she experienced nausea and vomiting and also had to reduce her protein intake still further to control phenylalanine levels.

During this difficult time Barbara required lots of support to help manage her diet – at least three telephone contacts per week. In addition to a phe-free amino acid supplement and a vitamin/mineral supplement, tyrosine supplementation was started at 16 weeks' gestation. From 20 weeks' gestation, protein (phenylalanine) tolerance starts to increase due to the growing fetus size and the fetal liver starting to produce the phenylalanine hydroxylase enzyme. During this time of increased phe tolerance, Barbara required further education on ways of incorporating the additional protein in her diet.

At 38 weeks' gestation, Barbara developed gestational diabetes and her labour was induced due to very high blood glucose levels.

After the birth the dietitian ensured the baby's Guthrie result (plasma phe level) was normal and reported this to Barbara. She also checked records of the baby's head circumference, weight and length. The baby was reviewed by the paediatrician at 6 weeks of age and will be assessed further by a clinical psychologist at 1 year, 4 years, 8 years and 14 years of age to check developmental progress. After delivery Barbara was encouraged to return to a normal unrestricted diet and to ensure that she had a balanced diet to support breast feeding.

3.6 Provision of dietitian-led clinics

Dietitian-led clinics are increasingly being established. They may be held in collaboration with doctors and clinical nurse specialists or solely by dietitians. These clinics may be particularly useful for management of patients whose treatment is mainly dietary (e.g. PKU, MCADD).

Example of a dietitian/CNS-led clinic

At London GOSH a dietitian/CNS-led group clinic for PKU has been established. Groups of similarly aged patients with PKU and their families attend together to undertake education on different topics. A pre-clinic questionnaire is completed by the dietetic assistant on the telephone to identify dietary and other problems, allowing more time for discussion at the clinic.

3.7 Education and training for health professionals

This is a major aspect of the work and includes the following:

- Development of educational materials such as diet sheets, information leaflets specific to particular disorders, and visual aids in order to support other professionals looking after IMD patients.
- Formal and informal training on IMDs to dietitians and other health professionals (e.g. medical, nursing, pharmacy, allied health professionals).
- Mentorship and clinical supervision for non-specialist dietitians.

3.8 Audit, research and consultancy work

This includes the following:

- Development and evaluation of new dietetic treatment regimens, treatment guidelines and protocols.
- Audit and research.
- Provision of professional advice to voluntary organisations (parents' support groups for IMDs, e.g. NSPKU, CLIMB).
- Provision of advice on IEM to the manufacturers of specialised metabolic dietetic products (e.g. advising on development of new products).

4 Education and professional development

4.1 Education and training reported by UK dietitians from survey

Nearly all of the respondents reported that their professional qualifications included a primary degree, and most had a postgraduate diploma in dietetics. Nearly half of respondents had or were in the process of getting a higher degree. The formal training in IMDs included:

- Experience gained via clinical practice, including specific rotations in metabolic dietetics
- Advanced Course in Paediatric Dietetics – Module 4
- SHS study days and meetings
- BIMDG study days and BIMDG dietitians subgroup study days
- SSIEM (Society for the Study of Inborn Errors of Metabolism) meetings including international dietitians' sessions.

Most dietitians came to work in IMDs from other paediatric dietetic posts, both general and in other specialist areas such as liver disease.

The survey showed their formal training in IMDs was limited. A few have participated in training rotations at the specialist centres, but most received training and gained experience on the job, which they supplemented as far as they could by training days such as those provided by the BIMDG. Dietetic posts offering training in IMDs are very limited. Currently only two specialist centres are known to have rotation training posts for their own staff (London GOSH and Manchester).

An educational opportunity which was highly valued by survey respondents was the current three-day Module 4 of the Advanced Course in Paediatric Dietetics, which is run by the Paediatric Group of the British Dietetic Association. Module 4 focuses on the practical dietary management of IMDs. The Paediatric Dietetics course team is currently working with the University of Plymouth to develop this module further to Master's level, so that it forms part of a Master's degree. This course would have extended content building on the current Module 4, and would include a total of about 200 hours study, with face-to-face teaching and some preparatory and follow-up study in the practitioner's service location. This venture provides an exciting opportunity for further developing and formalising the work of IMD dietitians.

The BIMDG dietitians subgroup also plays an important role in networking and providing professional support. This is mainly done by group email and study days.

5 Recommendations

1 Staffing

1. The role of dietitians is highly specialised and integral to the IMD service. There should be a specialist dietitian post in every centre, with more than one in the main centres. The numbers of specialist dietitians required will depend on the patient case mix. The staffing profile should consider using an appropriate mix of staff such as dietetic assistants, senior dietitians, specialist dietitians, advanced practitioners and consultant dietitians.
2. There are opportunities for dietitians to take on substantial areas of the service. However, their extensive roles need to be properly recognised and time made available for them to be undertaken properly.
3. Specialist metabolic dietitians also need to be adequately resourced to undertake organisational work in developing networks and protocols with peripheral services, education, audit, research and CPD.
4. It would be advantageous to train more dietitians to undertake these roles – but as a prerequisite for this, education should be developed further and formalised.

2 Education

1. There should be a working party including workforce development members to develop and implement educational programmes and training based on required competencies and predicted workforce requirements. This should include consideration of the following elements:

   - There should be an agreed formal training programme that includes theoretical, practical and professional aspects of the work. This should be developed to include documentation of education by the trainee.
   - Additional specialist dietitian posts in this area need to be created so those in training can have an expectation of a post being available.
   - Dietitians in training and others already in post must be supported to undertake more formal education – recognising that this is highly specialised and cannot be undertaken simply within the home service.

- The new Master's course should be supported.
- There should be more formal training rotations that take in a period of training at one of the main specialist centres. These centres should be formally recompensed for the time they spend teaching.
- Each region / specialist centre should have a specialist dietitian with a lead role for education in IMDs.
- Specialist dietitians must have the necessary time and resources to undertake teaching.

9 Voluntary organisations

Introduction

A focus group for representatives of voluntary organisations for people with IMDs was held on 23 June 2005. Those present included the following:

Hilary Burton	Consultant in Public Health Medicine, PHGU
Tanya Collin-Histed	Executive Committee Member, UK Gaucher Association
Brendan Gogarty	Public Involvement Officer, PHGU
Anne Hale	Executive Director, Global Organisation for Lysosomal Diseases
Steve Hannigan	Executive Director, CLIMB
Christine Lavery	Chief Executive, Society for Mucopolysaccharide Disease
Ann Phillips	President/Co-founder, Association of Glycogen Storage Disease.

Following presentation of the background to the work and some of the main findings of the services review, the group was asked to discuss their experiences of the services and their views on unmet needs for service users, focusing on diagnosis, initial treatment and long-term care. They were then asked to make recommendations on ways in which the services could be developed and improved.

Main unmet needs and recommendations

2.1 Diagnosis and misdiagnosis

There are regularly problems of misdiagnosis and lengthy time-lags before a diagnosis is made. This is often due to difficulties that non-specialist GPs and other practitioners have in recognising rare disorders that they are likely never to have seen before. Once someone suspects an IMD, it often takes a long time to get the relevant testing done. Testing may be slow. This may be a problem of out-of-date equipment or having to wait for a batch of samples before running the rest; sometimes it is because the laboratory service has only one tandem mass spectrometer and there is no back-up if it breaks down.

The next problem that patients and families encounter is communication during the time of the diagnosis. There are often problems of parents being given erroneous or imprecise diagnosis. This can lead to much distress as they look conditions up on the internet and see depressing and shocking information. This might turn out to be misleading or untrue when the final detailed diagnosis is made. There are delays in getting supporting information about the condition to the patient and parents. The voluntary groups thought that parents should only be told in general terms about the tests that are being done or what is suspected. Only when a precise diagnosis is known, and the appropriate information about the condition has been sought by the health professional, should the exact diagnosis be given to the parents. This should be immediately supported by information about the condition and the contact details of the relevant voluntary organisation. It was thought that this could be expedited by laboratories including information with the diagnostic result when a positive result is returned.

In summary, as with many other rare and serious diseases, voluntary groups thought that there should be standards around the process of communication of a diagnosis.

2.2 Initial treatment and care

Quote from McArdle perspective

This is often very poor indeed or non-existent. Quite often more harm is done than good. Many consultants who get involved in diagnosis are excited about finding a rare disorder but have no experience of it. They may only ever see one or two cases in their careers. There is a tendency to tell the patient that nothing can be done.

Representatives thought that quite often there was a reluctance to refer to the relevant expert owing to:

- lack of knowledge about the condition
- rarity of conditions
- lack of knowledge about the best expert services
- concern over expense
- desire to hang on to interesting cases.

They thought that there should be nationally defined care pathways for each condition (some examples are provided by MPS) which start at the time of diagnosis and cover specialist referral and management. In general, the time from diagnosis to getting to see a specialist is too long. Information about how to access these care pathways should be sent out to the health professional with any positive diagnostic test result.

Specialist services need to be available and accessible from the patient's home. But this is frequently not the case. The representative from CLIMB, the umbrella group for IMDs, thought that fewer than half of patients are looked after by specialist services and many have to travel long distances to access specialist services. Services should be commissioned on a geographical basis to cover the whole of the country.

The problem of lack of availability of services was made worse because services were often dependent on the availability of one consultant, making them very vulnerable to disruption when the individual is away, or, longer term, at retirement. Services need to be robust and comprehensive, including a whole multi-disciplinary team and sufficient clinical staff to provide cover on a 24-hour basis.

2.3 Standards of provision at out-patient services

Parents were concerned that there is no care or supervision for the child or for brothers and sisters when the child's case is being discussed. This means that either diseases and prognosis may be discussed in front of the child inappropriately, or both parents are not able to be present. It also means that brothers and sisters have to be left at home – a situation that parents do not like, firstly because finding care for them may be difficult and, more importantly, because it cuts them off from the attention focused on the sick child and provides no support for them in understanding what is happening. It was recommended that care should be provided in out-patient clinics for children and their siblings, to enable consultation with parents.

2.4 Ongoing care and support

'The patient is often left with little or no care and support. We need all patients to be referred to a specialist centre where there is in-depth knowledge of management or failing that good communication channels from specialist centres to local facilities to support patients near home'

Patients and families have long-term problems accessing adequate support. They experience:

- poor understanding of disease by local heath services, social services and education
- financial problems and problems getting allowances (voluntary organisations spend a

lot of time helping people with forms and being advocates for them)
- a major gap in respite care and education
- support services that are not comprehensive or integrated, do not reach the whole population, and are inconsistent.

They recommend that there should be good networks of care, including specialist centres and networks which include more local services, with professionals educated and supported by the specialist centre. In general, there needs to be more support for people with long-term disabilities on a national basis.

In IMD services voluntary groups noted a deficiency in psychology services, few transitional services for adolescence and a large gap in services for adults. All of these need to be developed for all regions.

Pre-implantation diagnosis is rarely available for couples with IMDs. It was thought that the reasons behind this should be explored further.

2.5 Organisational gaps

Disease register

There is no NHS disease register. However, much reliance is placed on the MPS register which is maintained by the voluntary organisation to cover London and Manchester patients and is thought to be 96 per cent correct. NHS services should invest in this, building on registers currently available through voluntary organisations.

Education of health professionals

Other health professionals and commissioners need to have more education about IMDs. Voluntary organisations could be involved in the provision and should be considered an integral part. However, they are not often asked.

3 Main recommendations

Many of the problems are characteristic problems of management of rare disorders.

1. Management of rare disorders should become a central concern of government and NHS, with ring-fenced money and a body (possibly an ombudsman) to raise awareness and champion issues.
2. Disease registers should be established and developed with proper funding to ensure quality, sustainability and accessibility.
3. There needs to be a programme of education for health professionals and commissioners. Voluntary organisations should be considered as providers. This would be supported by the voluntary sector, but would need some funding
4. Comprehensive and specialist services should be accessible to all patients. This will require:
   - development of robust services with specialist centres and networks to cover the UK geographically
   - development of a comprehensive network of transitional and adult services in association with main paediatric and laboratory centres
   - raising awareness of the presence of these services and prompting health professionals to refer patients on diagnosis
   - ensuring services are commissioned
   - specialist education and CPD programmes for all members of the multi-disciplinary team.

5. Voluntary organisations could help to increase pressure for development of services by supporting their members in seeking specialist management.
6. Professionals should work together with voluntary organisations to develop care pathways for all conditions, which would be centrally available and could be accessed and sent out by the laboratory when the diagnosis is made.
7. The issue of accessibility to pre-implantation genetic diagnosis should be investigated further.
8. Health services should work with voluntary organisations, social services and education to ensure comprehensive support services for those with long-term disabilities and health problems.

10 Specialist commissioning

What is specialist commissioning?

Definition of specialised services

The Department of Health defines specialised services as those with low patient numbers but which need a critical mass of patients to make treatment centres cost effective. This requires a population base that is much larger than those of individual PCTs (usually over 1 million). Currently, 36 specialised services are designated within the Specialised Services National Definition Set (2nd edition, 2002), although the usefulness of these definitions in reality has been questioned. IMDs are included under three of these sets:

- specialised services for women's health
- medical genetics
- specialised services for children.

Particular challenges for these services include training specialist staff, supporting high-quality research programmes, and making the best use of scarce resources like expertise, high-tech equipment and donated organs. Specialised services are subject to different commissioning (planning, procuring and monitoring) arrangements from other NHS services.

Organisation of Specialist Services Commissioning

National arrangements

The NSCAG was established in 1996 to facilitate the commissioning and funding of certain specialised services. Its aims are to ensure that patients with uncommon conditions have access to high-quality care, that financial and clinical risks to PCTs are minimised, and that provider units have sufficient resources to provide and develop their services. NSCAG has a series of very tight criteria for including specific conditions under its remit. At present, only LSDs, including Gaucher and Anderson-Fabry disease, are included from IMDs. NSCAG evaluates provider units applying to provide services, designates provider units for service provision, pays the costs of provider units whilst they are being evaluated, and produces service guidelines. For new services, additional funding is derived from NHS growth money or by a levy on PCTs up to the level of current NHS funding (if the service is or has been already provided by the NHS).

NSCAG has established a subgroup to advise on genetic disorders, the Genetics Commissioning Advisory Group (GenCAG); and the UK Genetic Testing Network (UKGTN), a subgroup of GenCAG, advises on genetic testing.

Other commissioning arrangements in England

Until 2002 specialised services were commissioned by eight Regional Specialist Commissioning Groups (RSCGs). These groups were based on the eight regional offices of the Department of Health. In April 2002 the NHS was reorganised after the report *Shifting the Balance of Power* was published, and PCTs (rather than health authorities) assumed responsibility for commissioning the bulk of NHS services. At the same time, the eight regional offices were absorbed into four Directorates of Health and Social Care, although the eight RSCGs remained. Specialised services were also removed from previous arrangements for cross-boundary funding. These changes prompted a review of specialised services commissioning in 2003. New guidance has been issued based on this review and the results of consultation. PCTs are responsible for establishing collaborative arrangements for commissioning specialised services. These collaborative

commissioning groups are known as Local Specialised Commissioning Groups (LSCGs) and Specialised Commissioning Groups (SCGs).
These groups aim to ensure that:

- service specifications include all aspects of the patient journey and take into account recommendations from NICE and other national groups or strategic frameworks
- there are agreed data sets to monitor activity and outcomes (clinical and financial)
- clinical and financial risk assessments have been carried out
- appropriate consortia and risk-sharing mechanisms are in place for very high-cost conditions with unpredictable and highly variable incidence rates.

LSCGs are usually coterminous with Strategic Health Authorities (10–15 PCTs) and have a planning population of around 1 million to 2 million. SCGs usually involve 2–5 LSCGs (45–50 PCTs), with a planning population of 3 million to 6 million. Each group is supported by its own commissioning team. All PCTs belong to LSCGs and all PCTs are represented on SCGs. Strategic Health Authorities are responsible for approving the arrangements and performance management.

Nevertheless, commissioning arrangements for the planning and procurement of services vary within individual SCGs, ranging from direct procurement by PCTs to risk sharing across all member PCTs. Specialist advisory groups may be established to support LSCGs and SCGs. A recent development in medical genetics has been the creation of formal, managed supra-regional networks of molecular genetic laboratories. The commissioning arrangements for these networks involve several SCGs, usually with one taking lead responsibility.

There is also no standardised approach to commissioning within SCGs. Each provider and commissioner therefore needs to understand what the local arrangements are. This complexity means that the implementation of national programmes can be challenging and is of great concern for IMDs.

Survey of specialist commissioning groups

A survey of SCGs was undertaken as part of the review process. Commissioners were asked about the following:

1. Local processes for commissioning IMDs.
2. How engaged specialist commissioners were with IMDs:
   - Whether there were any plans to review IMDs.
   - Service specifications and service level agreements (SLAs).
3. What issues were thought to be important when commissioning IMDs.
4. Whether existing arrangements were adequate and, if not, how they could be improved.

Thirty-one commissioners were contacted by email with a supporting letter and an electronic version of the questionnaire. Commissioners were reminded again if responses were not received within one month of the initial contact. A total of 17 replies (55%) was received from commissioners responsible for 184 PCTs. The results are summarised below.

1. Have IMDs been reviewed / are there any plans to review IMDs?

Four groups had reviewed IMDs and, of these, one was preparing a business case to establish a regional service for IMDs. None of the remaining groups was planning to review IMDs.

2. Are there separate service level agreements for adult and paediatric services?

None of the groups had separate service level agreements for adult or paediatric services.

3. *What mechanisms are there for dealing with cost pressures and service developments?*

There was general agreement that these were dealt with under existing arrangements on a case-by-case basis, unless specific business cases were received from providers or were dealt with through other mechanisms – most notably NSCAG (for LSDs). Three groups commented that other NHS issues were more likely to be prioritised over IMDs.

4. *How can commissioning for IMDs be influenced?*

A number of different responses were obtained. The majority felt that existing arrangements were generally adequate. NSCAG received a number of supportive comments (4/17), and others suggested that a supra-SCG network (other than NSCAG) might be useful (6/17). Two groups identified the need for clear and quantifiable guidance with protocols, quality standards and targets. Two groups felt that a specific national definition for IMDs would be helpful; one group even suggested a national service framework for IMDs and a national register to provide data on national incidence and prevalence. A number of groups highlighted a need for greater education for commissioners about IMDs to help with their work (4/17). One group believed that patient groups could be a powerful influence, although the mechanisms for this were unclear. One also felt that until a patient required specialist (and expensive) drug treatment, PCTs and commissioners were unlikely to consider IMDs as an issue, especially in light of their low incidence rates.

5. *What are the key issues for commissioning IMDs?*

A number of commissioners identified equity of access and evidence of clinical and cost effectiveness as key issues, as for other specialised services in general (4/17). Lack of information about the numbers of patients, where they were being treated and associated costs were also common concerns (5/17). A number highlighted funding issues and especially the cost implications of expensive enzyme replacement therapy (ERT) (6/17). Another group suggested that IMDs should be commissioned within their disease specialty and funded through payment by results. Other issues raised were lack of capacity, lack of knowledge about IMDs, workforce planning and sustainability, management of emergencies, and the transition from paediatric to adult care settings. One group commented that commissioning should be needs led.

6. *What improvements should be made to existing arrangement?*

Only one group felt that the existing mechanisms were 'not broken' and did not require fixing. The formation of a national network of commissioning groups for strategic planning and provision was a common theme from the responses received, with an identified lead for specific conditions (5/17). Funding through national capitation was proposed as one mechanism for funding, as long as there was equity of access to services. Risk-sharing mechanisms were also supported, and a number of groups felt that these should be strengthened. Again, the NSCAG model was identified as one potential model for supra-SCG service planning provision.

What are the key issues for IMD commissioning?

As described above, there is considerable variation in the way that specialised services are commissioned in England. This means that there are difficulties in developing a coherent national approach for IMDs, and problems for those planning or providing new services. Commissioners, providers, users and their representatives have identified a number of key problems. These include the following:

- Patients with IMDs may be managed by specialist providers or by generalists; this second group of patients need to be incorporated into specialist commissioning processes.

- IMD commissioning should move from service-based commissioning to needs-based commissioning.
- Adequate access to appropriate service centres.
- Ensuring that there are adequate adult services to manage the transition from paediatric to adult settings, especially as the outcomes for a number of IMDs are improving and more people are surviving into adulthood.
- Developing clinical networks and multi-disciplinary teams.
- Training and provision of key support staff, especially dieticians and nurses.
- Funding, especially for expensive ERT.
- Lack of information to support the commissioning process: numbers of patients, where they are treated, associated costs, quality and outcomes.
- Appropriate service planning for patients in a decentralised NHS.
- Training and workforce: both for metabolic physicians and allied professionals, especially specialist nurses and dieticians.
- NHS quality: equity of access for patients with rare disorders.

How to achieve forward progress

The process of commissioning for IMDs needs to be strengthened, so that patients with these disorders can receive accessible, high-quality care. NSCAG has provided one very successful mechanism for commissioning certain specialised services, most recently for the LSDs. However, it is unlikely that NSCAG will expand its remit to cover other IMDs. NSCAG requires very clear boundaries for services and, given the number and heterogeneity of other IMDs, it is very difficult for them to define appropriate limits. The other issue is that in the current decentralised NHS structure, NSCAG does not wish to further reduce the role of PCTs and the other specialised services commissioning groups.

Therefore, another model for non-NSCAG national commissioning would be useful. A recent collaboration for pulmonary hypertension may provide an alternative. Four lead commissioners to cover the whole of England were identified and a national service has been commissioned using this model. Other options to achieve progress are to focus on services for certain specific IMDs, with the aim of using them as catalysts for developing a range of services that would also be applicable to other IMDs.

Recommendations

The Department of Health and other national bodies (such as the Genetics Commissioning Advisory Group, Royal Colleges, professional associations such as the British Inherited Metabolic Disease Group and patient groups) have a key role in the following:

1. Raising the profile of inherited metabolic diseases and the importance of developing comprehensive and equitable specialist services across the UK.
2. Enabling the commissioning processes for inherited metabolic diseases through such mechanisms as:
   - a national supra-Specialised Commissioning Group network or other commissioning mechanism that includes service planning, procurement, provision and monitoring, risk-sharing and funding arrangements
   - enabling commissioning that is based on patient needs rather than current provision
   - consideration of inclusion of inherited metabolic diseases in the National Definitions Set for Specialised Services.
3. Providing support for specialist commissioners by:
   - education about inherited metabolic diseases

- developing information to support the commissioning processes, including minimum data sets, cost and quality information, number of patients and their use of specialist and other services.

4. Supporting developing services by:
   - establishing a national register for inherited metabolic diseases
   - setting up a working party including workforce development members to develop and implement educational programmes and training based on required competencies and predicted workforce requirements
   - supporting the infrastructure for a national laboratory and clinical network.

11 Conclusion: quality revisited

As a postscript we revisit our suggested standards for effective services, and some of the dimensions of quality suggested in Chapter 3, and consider to what extent they are met in the services as a whole as they are set up in the UK. We stress here that we have not investigated the clinical or laboratory services offered to individual patients, but rather have looked at the ways in which services are commissioned and set up across the UK. Findings from throughout the report which provide evidence for and against the various dimensions of high quality are summarised below.

Dimensions of quality	
Overall	No systematic planning or commissioning of services No database of patients
Effectiveness	
Availability of full specialist clinical and laboratory team to provide advice, support, and services for children, adolescents and adults	Only fully available in Manchester Willink and London Little access to psychologists as members of multi-disciplinary team
Clinicians and laboratory staff should have appropriate level of specialist education and undertake CPD	There is much concern that nurses and dietitians do not have formal specialist education and appropriate education opportunities, and most have learnt on the job Educational programmes to meet the specialist training needs of doctors need to be further developed and supported The programme of training for laboratory staff needs to be supported long term
There should be adequate professional support	There is support for all professionals from the BIMDG; this includes meetings and less formal email networks
Professionals should have adequate resources (including out-patient capacity) to undertake necessary volume of work	There is much evidence of unmet need through lack of capacity: waiting times, need to restrict access to local populations, lack of regional networks, lack of capacity to make home visits, insufficient dietetics support, responding to new cases arising from screening, delay in offering follow-up
Availability of full specialist clinical and laboratory team on a routine and emergency basis	Only at Manchester Willink and London GOSH
Specialist services should have a formal relationship with main feeder hospitals	Only ten services have relationships with some of their local hospitals
Specialist services should provide information on access for advice, testing and referral	Described as an unmet need
Specialists should provide education to help non-specialists recognise IMD and work together with tertiary services to manage their patients	Described as an unmet need
Development of protocols for joint	Described as an unmet need

management and shared care to provide ongoing care and manage crises as far as possible	
Development of shared care to oversee long-term care and ensure referral back to specialist services at times of particular concern (e.g. preparation for pregnancy, operations)	Formal arrangements in main centres only, especially those involved in NSCAG arrangements
Formal arrangements between specialist team and a wide range of other specialties such as cardiology, renal, obstetrics	Only in ten services
Formal arrangements between specialist IMD team and genetic services	Formal or good working arrangements described by most services
Specialist services have full range of information available to help patients make contact with relevant voluntary organisation	Not known
Services should be undertaking audit	Only 14 services
Services should be providing education and training programmes	Only two services provide formal specialist clinical training programmes
Services should be undertaking the necessary volume of work to maintain sufficient experience across the breadth of IMDs	Only six services had more than seven hundred patients
Efficiency	
What is the most efficient way to deliver a specialist service? Is there some element of critical mass for efficient services?	Services too thinly spread Nearly all services do not have critical mass; services are extremely vulnerable to changes and retirements of particular individual clinicians There is little collaboration (e.g. to develop patient information, guidelines, protocols); the laboratory network is an example of how this can be achieved
Accessibility	
Can patients get treatment when and where they need it? Are there barriers such as lack of information, distance, inability to pay, breakdown in service availability or waiting times?	Patients have to travel long distances Expense of travel Difficulty caring for other children when visiting service Local services are often unwilling to refer patients – either for diagnosis of during crisis Patients often have to contact specialist services themselves CLIMB – half patients do not receive specialist services Services do not meet the demand for patient information
Equity	
Are there failings in equity? Are some groups of patients treated differently on grounds of disease category, geography, age, ethnic group, etc.?	Large regional inequities in provision have been documented Patients with LSDs have access to NSCAG commissioned services, now set up and provided on a national basis with shared care arrangements;

	services for other conditions are not so well organised or funded Adults have poor access to services compared with children
Relevance	
Is the overall pattern and balance of services the best that could be achieved?	The overall services for the UK population has never been properly planned, but has developed largely on the basis of the interests of particular clinicians and provider trusts Commissioners have not commissioned services based on the needs of the population
Acceptability	
How is the service perceived by those who receive it (or might receive it)? Is it relevant, fair and responsive to demand? Are professionals satisfied with the service they are able to provide?	The provision of NHS care for patients with IMDs as a whole (covering both specialist and DGH elements) is generally seen as lacking by patients and voluntary groups Nurses and specialist dietitians do not feel they have had adequate education for the work they undertake Emergency care is provided by laboratory staff and clinicians on goodwill basis rather than on a formal basis

Conclusion

In conclusion, we acknowledge the commitment of individuals and teams of professionals in providing excellent services to their patients with IMDs as far as they are able. However, the lack of planning, resourcing and commissioning to provide comprehensive services to the entire population has meant that many patients do not have access to these services. Those that do must frequently find the services overstretched, limited in scope and unable to offer care tailored to their individual needs – including, for example, shared care arrangements which allow them to be looked after near home under the guidance and supervision of experts when necessary.

Parents of children, and patients themselves, have some of the biggest challenges of severe and chronic disease. Parents learn to provide complex treatment regimes; they recognise and deal with the acute crises that can occur at any time; they have to deal with a lot of other specialists, as their child has complications and problems with various organ systems; they may need to understand and take difficult decisions over the familial aspects of the condition. On top of all this, their energies may be almost totally consumed by coping with a child with a severe disability and all that entails in terms of everyday life, education and work opportunities.

We believe that the evidence is now available on which services suitable for this patient group could be developed in the UK by fairly modest investment and some reorganisation. Taking this opportunity now would enable the NHS to cope with likely increased demand arising from expanded screening services and new treatments, and provide a service that more nearly meets the needs of this population.

Appendix 1 Stakeholder group participant list

Dr Hilary Burton	Consultant in Public Health Medicine, Public Health Genetics Unit, Cambridge (Chairman)
Dr Anupam Chakrapani	Consultant in Inherited Metabolic Disorders, Birmingham Children's Hospital
Ms Alison Cousins	Clinical Nurse Specialist, The Charles Dent Metabolic Unit, National Hospital for Neurology, London
Dr Patrick Deegan	Senior Research Associate / Honorary Consultant in Metabolic Medicine, Department of Medicine, Addenbrooke's Hospital
Mrs Marjorie Dixon	Specialist Metabolic Dietitian, Dietetic Department, Great Ormond Street Hospital, London
Dr Godfrey Gillett	Consultant, Inherited Metabolic Disease in Adults Clinical Chemistry, Northern General Hospital, Sheffield
Professor Anne Green	Consultant Clinical Biochemist, Birmingham Children's Hospital NHS Trust
Mr Simon Griffith	Specialised Services Commissioning Lead, Norfolk Suffolk & Cambridge LSCG, Suffolk
Ms Paula Hallam	Metabolic Dietitian, The Charles Dent Metabolic Unit, National Hospital for Neurology, London
Mr Steve Hannigan	Executive Director, CLIMB National Information & Advice Centre for Metabolic Diseases, Crewe
Mrs Debbie Hilder	Information Analyst/Manager, Workforce Review Team, Winchester
Mr Alastair Kent	Director, Genetic Interest Group, London
Dr Philip Lee	Consultant in Metabolic Medicine, The Charles Dent Metabolic Unit, National Hospital for Neurology, London
Professor James Leonard	Professor of Paediatric Metabolic Disease, Biochemistry, Endocrinology & Metabolism Unit, Institute of Child Health, London
Dr Clodagh Loughrey	Consultant Chemical Pathologist, Belfast City Hospital, Belfast
Ms Sue Mather	Service Development Manager, Cumbria and Lancashire Specialised Services Commissioning Team, Preston
Mrs Sally Miles	Representative of Association for Glycogen Storage Disease (UK)
Mrs Ann Phillips	President/Co-founder Association for Glycogen Storage Disease (UK), Cheshire
Dr Peter Robinson	Consultant in Paediatric Metabolic Disease, Royal Hospital for Sick Children, Glasgow
Dr Simon Sanderson	Clinical Research Associate in Primary Care Genetics, Public Health Genetics Unit, Cambridge
Dr Graham Shortland	Chairman BIMDG, Consultant Paediatrician, Department of Child Health, University Hospital of Wales
Dr John Walter	Consultant Paediatrician, Willink Biochemical Genetics Unit, Royal Manchester Children's Hospital

Small-group meeting for specialist nurses

Participants and contributors of nursing case histories

Ms Alison Cousins	Clinical Nurse Specialist, The Charles Dent Metabolic Unit, National Hospital for Neurology, London
Ms Elin Davies-Pope	Clinical Research Nurse, Metabolic Medicine, Institute of Child Health, London
Ms Jane Gick	Paediatric Metabolic Nurse Specialist, Guys Hospital, London

Ms Joy Hardy	Clinical Nurse Specialist IMD, Birmingham Children's Hospital, Birmingham
Ms Jackie Imrie	Clinical Nurse Specialist - Niemann-Pick Disease, Willink Biochemical Genetics Unit, Royal Manchester Children's Hospital, Manchester
Ms Margaret Kenny	CNS Fabry, Hope Hospital, Salford Royal NHS Trust, Salford
Mr Alan Milligan	Clinical Nurse Specialist, LSDU, Royal Free Hospital, London
Ms Liz Morris	Lysosomal Disorders Specialist Nurse, Addenbrooke's NHS Trust, Cambridge
Ms Lorraine Thompson	Clinical Nurse Specialist, Fabry/LSD Services, Hope Hospital, Salford Royal NHS Trust, Salford

Small-group meeting for specialist dietitians

Participants and contributors of dietitian case histories

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Small-group meeting for representatives of voluntary organisations

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Appendix 3 Case histories

Case history 1 Management of a child with methylmalonic acidaemia (MMA)

This case report illustrates the complexity of inborn errors of metabolism and the large number of health professionals required for the care of affected patients. In this particular case such professionals have included: GP, consultant metabolic paediatrician, local consultant paediatrician, consultant community paediatrician, consultant paediatric surgeon, consultant paediatric nephrologists, consultant paediatric intensivists, consultant orthopaedic surgeon, consultant paediatric anaesthetist, consultant geneticist, clinical psychologist, specialist metabolic dietitian, specialist metabolic nursing staffing, community nursing staff, paediatric nursing staff on wards at both the district general and regional hospital, occupational therapist, physiotherapist, speech therapist, social worker and physiotherapist, In addition the diagnosis and biochemical monitoring of the patient has required the regional biochemical genetics laboratory.

Neville was an 11-year-old boy. He was the first child born to healthy, non-consanguineous parents. He was born by normal delivery at term following an uneventful pregnancy. During the first few weeks of life he had appeared well, but at one month he started to feed poorly and had occasional episodes of vomiting. After several visits to his GP he was referred to the local DGH. The paediatrician was concerned at his general degree at lethargy, weight loss and poor tone. He was admitted to the paediatric ward and had a number of routine investigations, but no diagnosis was forthcoming. He appeared to improve while in hospital and was discharged home after one week to be reviewed two weeks later.

After being sent home he seemed relatively well for the first few days. He then appeared to be developing a cold. However, over the following 24 hours his breathing became rapid and he stopped feeding. His parents brought him back to his local hospital in the early evening. He was admitted and treated with intravenous fluids and antibiotics. Routine investigations were again unhelpful and after a further two days he appeared somewhat better and was allowed home.

One week later he became increasingly drowsy and was again taken to hospital. On this occasion he was seen by another doctor who had previous experience in working at a centre for metabolic disease. She discussed his case with the regional inborn errors specialist, who arranged for a number of investigations. A diagnosis of methylmalonic acidaemia was then quickly made by the specialist laboratory and he was transferred to the PICU at the regional centre.

On arrival he was found to be encephalopathic and acidotic, and had a high blood ammonia. He required major intensive care support, including ventilation and haemfiltration. He made a gradual recovery and was commenced on a low-protein, high-calorie diet, vitamin B12 and l-carnitine. It was explained to his parents that he had a serious IMD. They were told that the condition could be associated with neurological and renal disease and needed lifelong treatment in order to limit further complications.

Unfortunately, over the next few months it became clear that his encephalopathy had resulted in serious neurological damage with significant changes affecting the basal ganglia on brain MRI. Due to poor oro-motor coordination, he was unable to feed normally, and after a period of nasogastric feeding required a gastrostomy and overnight pump feeds. He was referred to the community paediatric team for additional support at home.

Over the next decade Neville has managed well at home, but has required frequent clinic visits. He has had a number of acute admissions with metabolic acidosis and pancreatitis (a recognised complication), both to his local hospital and the specialist centre. As expected, he has developed severe renal impairment and will eventually need renal dialysis or renal transplant. He now has a

reasonable IQ but a severe movement disorder and is wheelchair bound. He has developed a progressive kyphoscoliosis.

Neville's parents requested prenatal diagnosis for their next pregnancy, which was found to be unaffected.

Neville has required the continued and regular input of a large number of professionals.. These include the specialist IMD team (medical, genetic, nursing, dietetic, psychology, laboratory); other specialist service (surgical, renal, orthopaedic, gastroenterology); community (medical, physiotherapy, occupational therapy, nursing, social services) and educational (psychology, schooling). His life expectancy is likely to be limited, but he may well survive into adult life.

Case history 2 Management of a young adult with medium chain acyl CoA dehydrogenase deficiency (MCADD)

John was a patient in his early 20s. Although otherwise thought to be well, he presented to the emergency department at his local hospital on three occasions with metabolic acidosis and encephalopathy. Medical staff thought that these were possibly alcohol-related events, but no definitive diagnosis was made in relation to the metabolic acidosis. On a fourth and final occasion, he presented with encephalopathy and died. The diagnosis of a possible fatty acid oxidation defect was made on post-mortem histology. This was later confirmed on genetic testing to be MCADD.

The specialist metabolic clinic then became involved because of the risk to family members. Subsequently, one sibling was identified with the same diagnosis; this was confirmed both genetically and biochemically. She had previously been asymptomatic with no hospital admissions and was unaware of the diagnosis. The metabolic service was able to provide information on the condition, lifestyle advice to avoid long-term fasting, and future advice regarding potential medical issues such as starvation if surgery was ever required. An emergency dietary regime was provided and the patient was given information to contact specialist services if required.

This case history shows the following key management points:

1. Metabolic disease can present at any age. Despite the fact that MCADD predominantly presents in the paediatric age range, it can present later and requires specialist management.
2. Once the diagnosis is made, simple clinical management can significantly improve outcomes with specialist advice.
3. Failure to make a diagnosis may lead to significant morbidity and mortality.
4. Awareness of metabolic disease is needed in the adult and paediatric medical communities.

Case history 3 Management of two contrasting patients with maternal PKU

A 19-year-old girl with PKU was re-referred to an adult clinic. She had been diagnosed on newborn screening and treated with a phenylalanine-restricted diet for the first 12 years of her life. She had normal schooling but was lost to follow-up by the paediatric department from 13 years onwards.

At 19 years, she was on a normal diet, including meat, dairy products and eggs. She was well, without any neurological abnormalities. Plasma phenylalanine was 1,140 μmol/l. She brought her 18-month-old son with her. He had been having myoclonic seizures for two to three months. He had no speech and was not walking. On examination, he had hypertelorism, epicanthic folds and microcephaly. He had a mild spastic quadriparesis. A Griffith's developmental assessment gave a general developmental quotient of 78. He was seen again when he was 4 years old for a McCarthy assessment, which was impossible to score because of behavioural problems. He was reviewed

again at 8 years. At that stage he was having special schooling, having a statement of his educational needs. A WISC III assessment gave a verbal IQ of 61, performance IQ of 66 and full-scale IQ of 61.

Another woman with PKU was born in 1969. She was diagnosed at five months because of developmental delay, and placed on a phenylalanine-restricted diet until she was 8 years old. She attended mainstream school but received extra help. She continued to attend the children's PKU clinic annually and at 18 years was transferred over to the adult services, remaining on a normal diet. Her IQ was measured at 81. She worked as a shop assistant. At 24 years, she married and a year later was admitted to restart a phenylalanine-restricted diet, conceiving four months later. She maintained phenylalanine levels between 60 and 400 µmol/l throughout the pregnancy, giving birth to a baby girl with a birth weight of 3.77kg. The daughter had a Griffith's developmental assessment at 1 year which gave a DQ (development quotient) of 115, a McCarthy assessment at 4 years which gave an IQ of 98 and a WISC III assessment at 8 years which gave a verbal IQ of 107, performance IQ of 104 and full-scale IQ of 106.

Case history 4 Management of a pregnant woman with ornithine carbamyl transferase deficiency (OCT)

A patient presented with a complex metabolic disorder requiring coordinated care between five clinical services.

OCT (ornithine carbamyl transferase) deficiency is an X-linked urea cycle defect (required for the removal of waste nitrogen as ammonia) that causes hyperammonaemia that can lead to severe brain damage. It is the commonest urea cycle defect. It is often a fatal condition in males, resulting in death in the neonatal period or in infancy, irrespective of medical treatment. In females the manifestations are variable, ranging from death in the newborn period (severe) to acute metabolic decompensation in childhood (intermediate/mild) to asymptomatic. Liver transplantation offers a more definite treatment that can allow good outcome. Even apparently asymptomatic females can suddenly develop potentially fatal hyperammonaemia in response to stress at any time in life. Childbirth is particularly stressful from a metabolic point of view, and a number of previously asymptomatic females with OTC deficiency are known to have died from fatal metabolic decompensation in the first few days after delivery.

Management of symptomatic cases requires treatment with low-protein diet and drugs to prevent the build-up of high ammonia levels. This needs expert dietary management, and biomedical monitoring under the care of a metabolic physician.

Patient Anthea is a 19-year-old female with OTC deficiency who first presented with acute hyperammonaemia in early childhood. She was treated with a protein-restricted diet and drugs to reduce hyperammonaemia (sodium benzoate, sodium phenylbutyrate and arginine) under the IMD team. This prevented severe brain damage, and she made relatively good progress at school. She was able to take up employment as a hairdresser in the late teens, although she continued having occasional episodes of metabolic decompensation associated with acute intercurrent illnesses requiring hospitalisation for intravenous therapy. She underwent genetic counselling regarding the risks of having an affected child (50%) and was also warned about the potential dangers to her life immediately after childbirth.

Despite this advice, Anthea presented to the IMD team at the age of 19 years with a concealed pregnancy; on ultrasound scan she was found to be 18 weeks pregnant. She fully understood the implications this pregnancy had for her baby and herself. There were two urgent issues that had to be addressed immediately:

1. Antenatal diagnosis of OTC deficiency for the fetus in view of the fatal outcome in affected males and many affected females.
2. Anthea's care after delivery, which would require:
   - intensive (4–6 hourly) monitoring of blood ammonia levels over the first week after delivery requiring hospitalisation
   - intravenous medications for the first few days
   - readiness for immediate haemodialysis if the ammonia levels rose despite medical therapy.

An immediate referral was made to the genetics services for antenatal diagnosis. Simultaneously, a referral was made to the obstetric services for planned delivery and immediate post-delivery care. Contact was also made with the renal and liver units for help with Anthea's medical management after delivery and for possible haemodialysis. Within a few days she was seen at the joint genetic/obstetric clinic and by the joint renal/obstetric clinic to plan further management.

DNA testing revealed an affected male fetus and a decision to perform a termination was made. A detailed management protocol was prepared by the clinical, biochemical and dietetic IMD teams in liaison with the obstetricians, nephrologists and hepatologists. The protocol was complex, requiring drug, diet and regular blood monitoring and required precise implementation in order to prevent a fatal outcome for the patient. The procedure was undertaken at 22 weeks pregnancy at the obstetric unit. A dialysis line was inserted at the same time pre-emptively, and the patient was transferred to the renal unit for further monitoring and treatment. Intravenous medical therapy was commenced in consultation with the IMD team. Four- to six-hourly ammonia levels were performed for the first four days and remained stable. Intravenous medical therapy was switched to oral on the advice of the IMD team after day 4 post-op. Subsequent ammonia levels were monitored twice daily and the patient was discharged home on day 8 with a plan to perform twice-weekly ammonia levels for six weeks; this further management was supervised by the metabolic team and her usual low-protein diet was reintroduced. Anthea recovered well and did not develop any sequelae. She was subsequently referred to the liver team for a consultation about the possibility of future treatment with a liver transplant. Her continued follow-up rests with the IMD team.

Appendix 4 Resident regional population and sources

	Population 0–19	Population 20+	Total
	1000s	1000s	1000s
Northeast	624.3	1915.1	2539.4
Northwest	1730.8	5073.7	6804.5
Yorkshire and the Humber	1268	3741.3	5009.3
East Midlands	1052.2	3200.1	4252.3
West Midlands	1361.5	3958.4	5319.9
East of England	1344.2	4118.7	5462.9
London and Southeast	3789.5	11678.7	15468.2
Southwest	1179.8	3819.5	4999.3
Wales	732.9	2205.1	2938
Scotland	1199.9	3878.5	5078.4
Northern Ireland	489.937	1220.385	1710.322
Total	14773.037	44809.485	59582.52

Sources

1. Office of National Statistics Mid-2003 Population Estimates. Quinary age groups and sex for local authorities in England and Wales; estimated resident population

2. Registrar General for Scotland. Mid 2004 population estimates

3. The Northern Ireland Statistics and Research Agency. General Register Office. Mid year estimates, 2004

Public Health Genetics

The Public Health Genetics Unit, funded by the Department of Health, is a national leader in public health genetics. Since it was established in 1997 PHGU has played a significant role in the translation of genome-based knowledge and technologies for the benefit of population health.

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