# 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<br>School of Clinical Medical Sciences, Newcastle upon Tyne |
| Northwest | Manchester Lysosomal Storage Disorder Service<br>Manchester Willink Biochemical Genetics Unit<br>Royal Liverpool Children's Hospital, Alder Hey |
| Yorkshire and Humber | St Luke's Hospital, Bradford<br>Northern General Hospital, Sheffield<br>Sheffield Children's NHS Trust<br>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<br>London Royal Free Hospital<br>London Great Ormond Street Hospital for Children<br>London University College Hospital |
| Southwest | Bristol Royal Hospital for Children<br>North Bristol NHS Trust, Southmead Hospital |
| Wales | University Hospital of Wales, Cardiff |
| Scotland | Royal Hospital for Sick Children, Edinburgh<br>West of Scotland Royal Hospital for Sick Children, Glasgow<br>Royal Aberdeen Children's Hospital<br>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

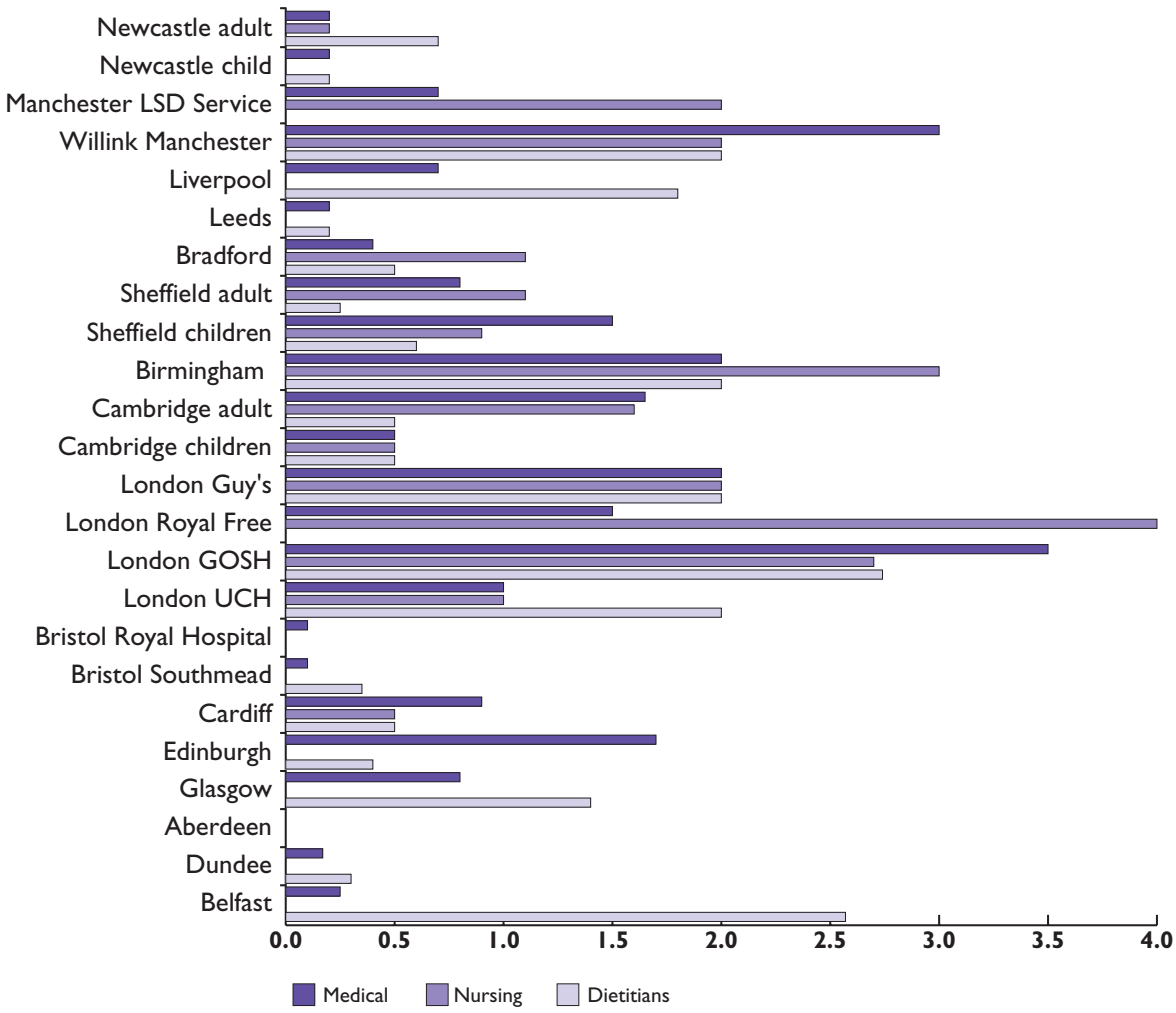
The total workforce is:

- 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.

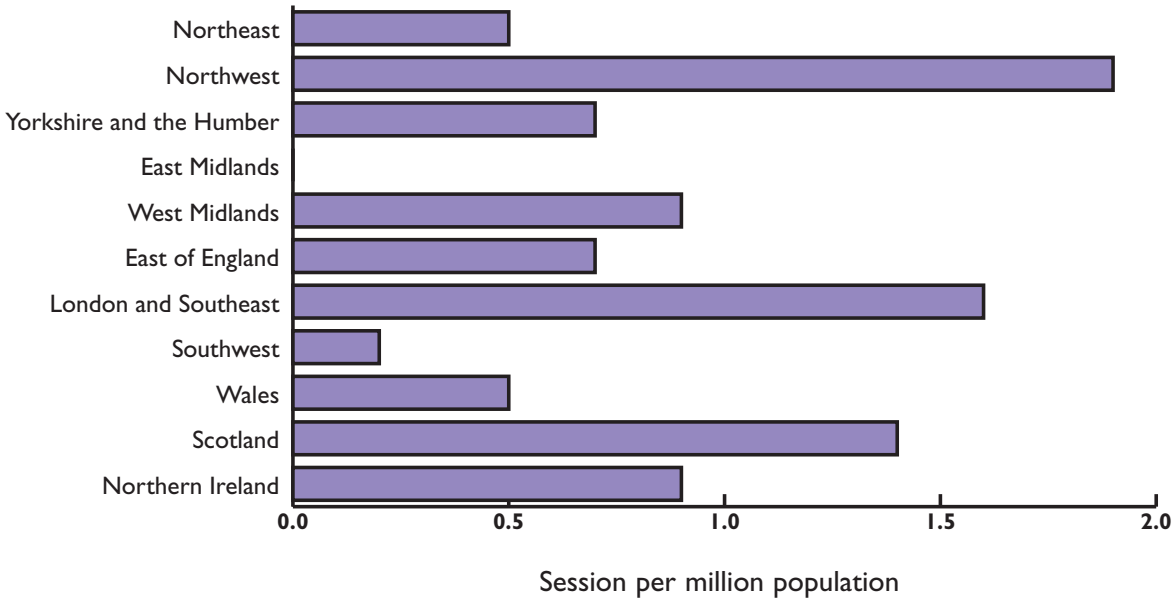
**Regional variability in provision**

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).

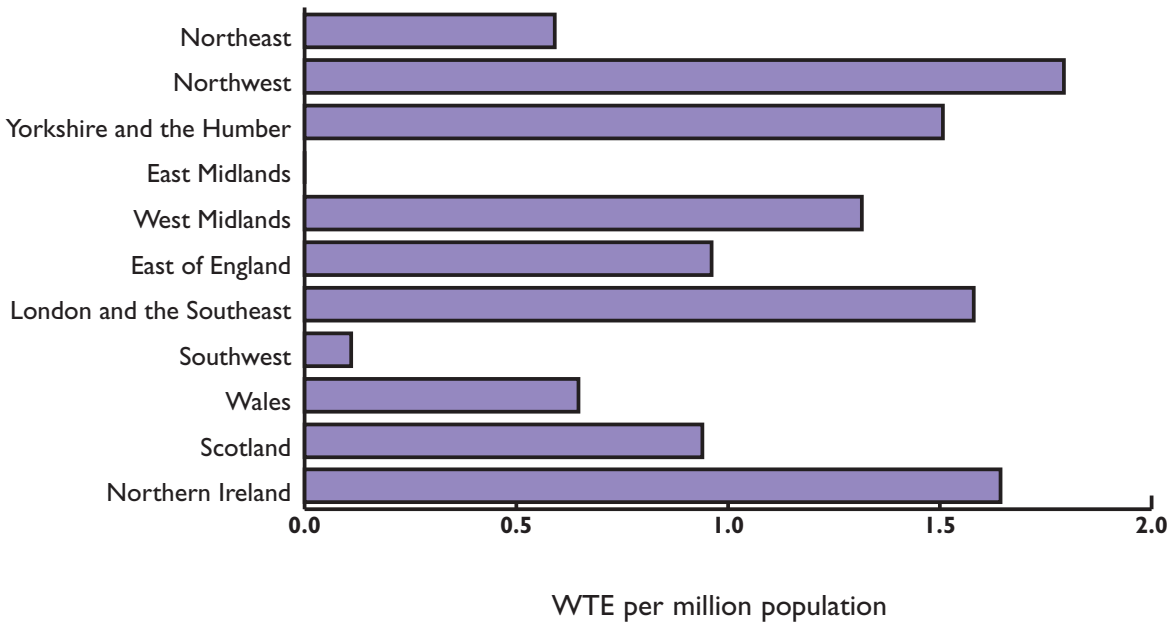
**Figure 1.2 Average total number of out-patient sessions per week per million population by region**




*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.

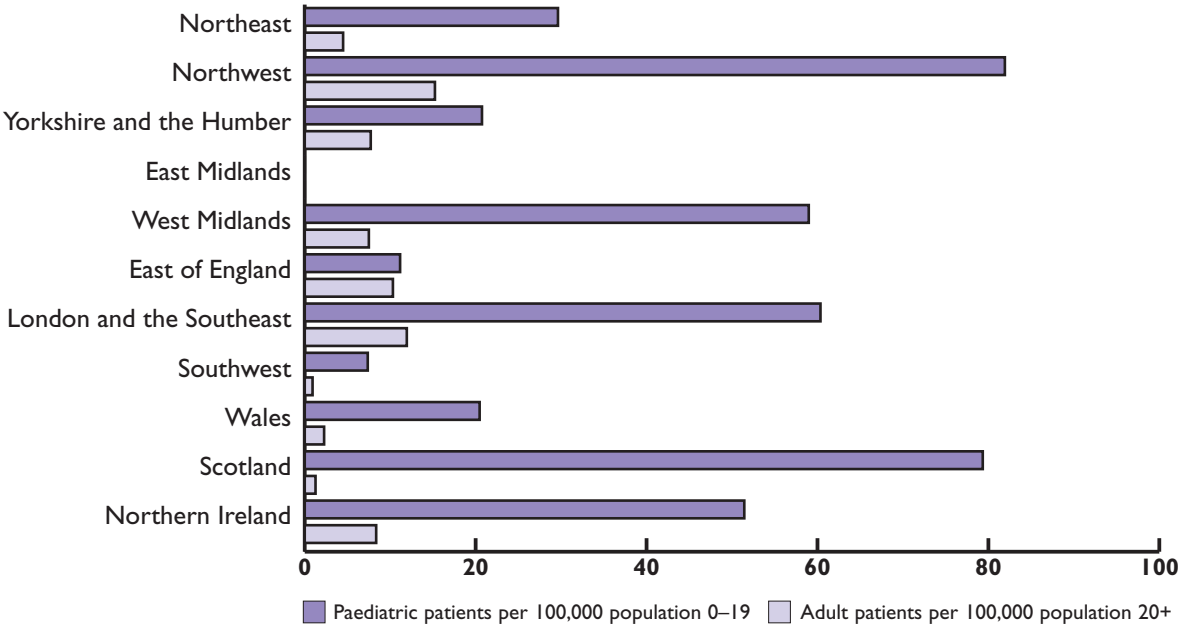
**Figure 1.3 Total clinical workforce (WTE per million population) by region**



*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<br>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