A report on genetic Registers

Based on the Report of the Clinical Genetics Society Working Party¹

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A Register may be defined as a record in which regular entry is made of details of any kind sufficiently important to be exactly recorded (Shorter Oxford Dictionary). Genetic Registers range from simple card index systems of patients in whom a geneticist has a special interest, to elaborate computerised systems which may include a great deal of personal, medical, and genetic information on affected individuals and their relatives. There are a number of different types of genetic Registers, but our attention has been mainly directed to Registers designed specifically for the *prevention* of genetic disease, since it is in this area that most concern regarding feasibility, acceptability, and confidentiality has been voiced. In recent years there has been growing interest in establishing such Registers as a means of improving the ascertainment and follow-up of individuals in the population who are at risk of transmitting a serious genetic disorder to their offspring.

In 1977 the Committee of the Clinical Genetics Society formed a Working Party in order specifically:

- (a) To consider the nature of genetic Registers.
- (b) To consider the value and potential application of such Registers, particularly with regard to the prevention of genetic disease.
- (c) To consider genetic Registers with regard to: (i) specific genetic disorders such as Huntington's chorea; (ii) genetic disorders in general where relatives may be at high risk.
- (d) To consider both the feasibility and acceptability of genetic Register systems organised: (i) on a national basis; and (ii) on a more local basis.
- (e) To make recommendations.

The Working Party met on several occasions to discuss these matters and this paper represents a summary of some of the main conclusions in the Report, which was presented to the Society in July 1978.

The nature and purpose of genetic Registers

At present, 38 centres in Britain maintain Registers primarily concerned with genetic disease. These Registers can conveniently be considered under five different headings, though they are not mutually exclusive.

(1) *Clinical (or Therapeutic) Registers*, to facilitate the follow-up and recall of individuals for therapeutic reasons, or when relevant preclinical or prenatal diagnostic tests become available.

(2) *Reference Registers*, to store clinical and laboratory data on individuals with genetic disease, so that the diagnosis in a new case might be confirmed by reference to previous cases.

(3) *Registers for Monitoring Services*, to assess the results of genetic counselling and prenatal diagnosis.

(4) *Research Registers*, to store and analyse epidemiological data, or to determine the natural history of particular genetic disorders.

(5) *Preventive Registers*, to improve the ascertainment and follow-up of individuals at risk of transmitting a serious genetic disorder to their offspring, so that they may be offered genetic counselling and prenatal diagnosis where possible.

Of the 90 Registers currently maintained in Britain, 11 would be considered Clinical/Therapeutic, 15 Reference, 23 Monitoring, 29 Research, and 12 Preventive.

Registers and the prevention of genetic disease

The results of several theoretical studies have shown that unifactorial disorders, especially autosomal domi-

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nant and X-linked recessive disorders, provide the best scope for preventing genetic disease (Smith, 1970; Holloway and Smith, 1973; Fraser, 1974). Follow-up studies of individuals referred for genetic counselling have confirmed these theoretical findings, but have also shown that over 85% of relatives deemed to be at high risk (greater than 1 in 10) of having a child with a serious genetic disorder have never been given counselling and are unaware of the risks (Emery and Smith, 1970; Emery, 1972). Further, a number of affected children were born to parents who, *a priori*, were at high risk of having an affected child, which might have been prevented if the parents had had genetic counselling. The ascertainment and follow-up of individuals at risk in the population is, therefore, crucial in the prevention of genetic disease, and it is in this regard that a genetic Register system can be of particular value, especially for the follow-up of those who are currently too young for genetic counselling. A WHO Scientific Group (World Health Organization, 1972) has, in fact, recommended that medical genetics centres should set up Registers of genetically determined disorders specifically for the purpose of preventing genetic disease.

Particular consideration was given to three computerised genetic Register systems designed, at least in part, for the purpose of preventing genetic disease: the Edinburgh RAPID system, the Indiana MEGADAT system, and the Belgian National Register.

(1) THE EDINBURGH RAPID SYSTEM

A Register system specifically designed as a means of ascertaining and preventing genetic disease was first established in Edinburgh in 1970 under the acronym RAPID (Register for the Ascertainment and Prevention of Inherited Disease), and has been fully operational for the last two years (Emery *et al.*, 1974; Emery, 1976). The organisation of the RAPID system can be conveniently considered under two main headings: ascertainment, contact, and follow-up of individuals at risk; and the recording, storage, and retrieval of family data.

(a) Ascertainment, contact, and follow-up

Ascertainment of individuals at risk of having a child with a serious genetic disorder may be direct or indirect. *Direct* ascertainment is when the index case is brought to attention as a result of routine diagnosis. *Indirect* ascertainment is when index cases are obtained through public health records and statutory registers, and therefore without the individual's knowledge. Indirect ascertainment raises a number of difficult ethical problems, and is also extremely time-consuming and relatively unproductive. This form of ascertainment has therefore been abandoned, and individuals at risk are now only ascertained directly

through special clinics, which include a large proportion of inherited disorders (for example, neurology, haematology, and ophthalmology), special schools (for example, for the mentally handicapped, blind, and profoundly deaf), and various voluntary patient organisations.

Having ascertained individuals at risk of having affected children, at present only those at high risk (greater than 1 in 10) are contacted and followed-up. Relatives at risk are contacted only with the express permission of both the index case and the relative's family doctor, and, at least in the first instance, contact is best arranged directly by the family doctor or health visitor. This is considered important, as there may be factors unknown to the geneticist or index case which might make it unnecessary, or even imprudent, to contact certain family members.

At present, any individual has the prerogative to withhold knowledge of his medical condition from his relatives if he so wishes, though in taking this attitude he accepts a heavy responsibility if such information might prevent the birth of an affected child in another branch of the family. No individuals are included in the RAPID system, nor are their relatives contacted, without written permission, a specially designed form being used for this purpose. This form is signed only after the Register system has been explained and the implications discussed with the individual concerned.

(b) Recording, storage, and retrieval of family data

For ease of storage and retrieval of family data, the RAPID system has been computerised. The present file system can store data on 25 000 to 30 000 individuals. Access to the data is through an interactive teletype terminal using the Edinburgh Multi-Access System (EMAS) on an ICL 4-75 computer. The computer program is in FORTRAN, details of which are available (Moores and Emery, 1976). To maintain strict confidentiality of the information in the Register, a number of security checks have been incorporated into the system and the various recommendations of the Younger Report have been adopted (Computers and Privacy, 1975).

Currently, information on over 700 individuals is stored in the RAPID system, involving 52 different disorders, though about 80% of those on the Register can be accounted for by relatively few disorders (Table 1).

(2) THE INDIANA MEGADAT SYSTEM

MEGADATS (Medical Genetics Acquisition and Data Transmission System) is a computerised system for the collection and processing of information on families with genetic disorders. It was set up by the Indiana Human Genetics Centre using information on

Table 1 Proportions (%) of individuals at risk on RAPID

Disorder	% of individuals
<i>Autosomal dominants</i>	
Huntington's chorea	15
Polycystic kidney disease	9
Myotonic dystrophy	5
Neurofibromatosis	3
Polyposis coli	2
Retinitis pigmentosa	2
Marfan's syndrome	2
<i>X-linked recessives</i>	
Haemophilia (A and B)	27
Duchenne muscular dystrophy	7
Retinitis pigmentosa	3
<i>Familial translocation</i>	
Down's syndrome	3

families seen for genetic diagnosis, counselling, or for research studies, and in 1975 it incorporated data on a third of a million individuals from over 15 000 families, and is growing by about 1500 families per year (Merritt *et al.*, 1976).

MEGADATS was set up to facilitate the storage, updating, and processing of data collected for use in medical genetic services as well as for research. The aims have been set out as being:

- (1) To facilitate the diagnosis of inherited disorders.
- (2) To provide greater insight into the genetics of complex problems with major genetic components, and thereby aid genetic counselling, early diagnosis, and preventive therapy.
- (3) To show the value of these data to practitioners through ready access, cost-effectiveness, and patient response to counselling.
- (4) To encourage the use of pooled data from specialised populations with a high risk of certain specified diseases, both simply inherited and of unknown complex aetiology.
- (5) To show the feasibility of collecting, recording, and using this highly personal and sensitive data while fully protecting confidentiality and individual rights.
- (6) To permit the retrieval of information on heterogeneity, genetic linkage, and chromosome mapping that will assist in diagnosis and counselling by providing improved risk estimates.

The system has been built up over the last 14 years. Initially, medical genetics department files were stored on magnetic tape and updated at 6 to 12 month intervals. They were processed on an IBM 7040 computer in the Research Computation Centre of the University Medical Centre by batch processing. The data were used for biometrical studies, statistical, and genetic analyses.

By 1975, a PDP-11/45, coupled to a PDP-11/05 for laboratory automation, was also in use. This is

used interactively and includes, among a wide variety of facilities, an XY plotter and XY digitiser. It is linked to the Indiana University regional computer network. In order to retrieve information in an ordered manner, a data base management system (S2K) is used, which facilitates retrieval of pedigree material. Security is maintained by password control to the data base and to each component.

MEGADATS is thus a complex computer system for the storage and retrieval of a variety of genetic information on individual families. Such information can be used for both clinical and research purposes.

(3) THE BELGIAN NATIONAL REGISTER

This is a Register containing data on all persons referred to any of the seven Belgian medical genetic centres, which amounts to about 5000 to 6000 people a year (Vlietinck and Van den Berghe, 1976). There is a master file containing a unique identification of each individual, but this is available only to the referring centre and is otherwise used only to ensure that a new entry is not already on the file. Other data, such as sex, birth place, consanguinity, non-paternity, adoption, mode of ascertainment, ethnic origin, pedigree, and medical information, are kept in further files and are available to all the participating centres. Health insurance companies in Belgium maintain Registers of individuals with malformations, cancer, tuberculosis, and mental illness. There is no link between these and the genetic Register, but the former can provide epidemiological data and, in the case of one of the larger Registers, records its data in a similar manner to the genetic Register. Other programs cater for pedigree analysis, linkage, recurrence risk calculations, and statistical analyses. Thus, this Register is very similar in many ways to MEGADATS. However, unlike MEGADATS, it is a national Register and should therefore be able to provide epidemiological data relating to the entire population.

Registers for specific genetic disorders and for genetic disorders in general

A number of Registers for specific genetic disorders already exist, for example, Registers for haemophilia (several centres), polyposis coli (as at St. Mark's Hospital, London), and phenylketonuria (as at the Institute of Child Health, London). Other genetic disorders for which Registers already exist, or are being considered, include Huntington's chorea, polycystic kidney disease, myotonic dystrophy, retinitis pigmentosa, and Duchenne muscular dystrophy.

Registers for specific genetic disorders have certain advantages over more general genetic Registers. There is likely to be increased accuracy of diagnosis and better quality of information, greater familiarity of the

Unit maintaining the Register with problems resulting from the disorder, more complete ascertainment in a region¹, and the possibility of closer integration between genetic matters and the general management of the disorder.

However, against these advantages must be set the disadvantages of fragmentation resulting from different Registers being kept by different departments, and lack of standardisation, since the form of a Register may differ widely depending on the nature of the disease. In setting up a specific disease Register, it is important that the system of data recording be compatible with more general Registers, as well as with other specific disease Registers.

Feasibility of genetic Registers

Although several genetic Registers have now been established, there have been very few feasibility studies published. One reason for this probably lies in the rather imprecise aims of many of the Registers established so far.

COST/BENEFIT

Cost/benefit analysis is notoriously difficult in medicine, and perhaps especially so in the case of such problems as genetic Registers. Emery estimated in 1974 that the overall cost of RAPID, exclusive of salaries, was £1.09 per individual counselled. By 1977 this figure had risen to £3.50 per individual. These figures include the costs of correspondence and travel involved in family visiting, as well as computing, and were higher for consultants² than for their relatives. Thus, costs for any other Register would depend on the ratio of these two categories of individuals counselled. To these administrative and computer costs must be added the salaries of a medical geneticist, a clerk/computer operator, and a field worker. This is the staff considered necessary to maintain a Register for a population of a million, which might generate approximately 200 new families each year. Extension to a larger population would require additional resources in regard to field workers and medical geneticists.

Benefit is far more difficult to estimate in financial terms, since it depends on how many affected births will be prevented through genetic counselling, and also on the wide variation in cost to the community of caring for patients with different serious genetic disorders.

Rough estimates of the number of cases of some genetic disorders which might be prevented by genetic counselling in the United Kingdom each year are given

Table 2 *Approximate numbers of cases of some genetic disorders which might be prevented by genetic counselling in the United Kingdom each year (Emery, 1978).*

Disorder	Birth frequency (per 1000 live births)	Estimated preventable cases each year
<i>Autosomal dominants</i>		
Huntington's chorea	0.50	350
Polycystic kidney disease	0.80	448
Myotonic dystrophy	0.20	126
Neurofibromatosis	0.40	140
Polypoid coli	0.10	49
Marfan's syndrome	0.04	22
<i>X-linked recessives</i>		
Haemophilia (A and B)	0.10	29
Duchenne muscular dystrophy	0.30	22

It is assumed that there are 700 000 live births (360 000 males) per year in the UK (based on data for 1975). Birth frequencies are based on various sources, but mainly Carter (1977), and in X-linked recessive disorders this refers to the frequency per 1000 live male births.

in Table 2, but these do not include any benefits that might accrue from population screening programmes. Since many of these disorders will cost the community, in medical and welfare services, considerably more than the expense of ascertainment and counselling, even if the latter is only partly effective it would seem likely that this approach could be well justified on economic grounds alone.

RESPONSIBILITY FOR GENETIC REGISTERS

A genetic Register covering a particular region would be most conveniently based in the principal medical genetic centre for that region. Because of the clinical nature of much of the data stored, and the probability that most genetic Registers that will be set up in this country will be for the purpose of improving ascertainment for genetic counselling, the appropriate individual to have overall responsibility for the Register would be a medical geneticist of consultant status, with the co-operation of appropriate community medicine staff.

ACCESS TO GENETIC REGISTERS

The question of access depends on the aims of the Register. A Register maintained purely for ascertainment and follow-up of individuals at risk, so that they can be offered genetic counselling, should only allow access to persons actually involved in genetic counselling. Persons able to retrieve information from the Register will be more narrowly defined than those who are allowed to enter information. As individuals at risk will not be confined to a particular health service region, it is essential to provide a service for genetic counsellors outside the region.

Registers with broader functions, such as the maintenance of epidemiological or research data, will need to provide wider access. This may require a more

¹In this Report, *region* is used as a term of convenience and is not necessarily meant to designate a specific administrative area within the NHS.

²A *consultant* is defined as the first member of a family who seeks genetic counselling. He may be healthy, affected, a preclinical case, or a carrier.

complex categorisation of types of worker granted access in relation to levels of information within the Register. For example, epidemiologists and most research workers may be granted access to statistical data but not to personal data. If individuals are to be identified to research workers, this would require the most stringent safeguards and the fully informed consent of the individuals concerned, or their guardians, on each separate occasion that the information was released. Probably the only really adequate safeguard for this type of access is that it should not be direct, but only through the centre in charge of the Register.

AVAILABILITY OF SUPPORT

Before initiating a genetic Register, it is essential to establish that adequate provision has been made for genetic counselling services, and for medical and social supportive help for those who are found to be at risk. The establishment of a Register will generate a work load which may well exceed the existing genetic services. Further, those ascertained as being at risk of having affected children may require additional support from the medical profession as well as the social services.

Acceptability of genetic Registers

The acceptability of genetic Registers to those most likely to be involved, namely consultands and their relatives and family doctors, is an important issue and was considered in some detail.

ACCEPTABILITY TO CONSULTANDS AND RELATIVES

Numerically, the most important groups of individuals likely to be concerned with acceptability are those who are already affected with a genetic disorder or are pre-clinical cases, and those who are carriers of X-linked recessive disorders. Wilkie and Sinclair (1977) studied acceptability in regard to RAPID and concluded that those involved with X-linked recessive disorders were those who were most in favour of genetic Registers. However, the advantages of counselling an individual at risk of developing a disorder such as Huntington's chorea, myotonic dystrophy, or neurofibromatosis may not always be evident to the individual concerned. The obvious advantage is that it may help prevent the disorder from being transmitted to subsequent generations. The main disadvantage is that since an effective treatment is not yet available for any of these disorders the knowledge that one may develop the disease may engender considerable distress. Such information may in some instances lead to marital disharmony, but the alternative of withholding information or erroneously reassuring a couple is to be

deprecated. An important function of a genetic Register should be to help detect individuals at risk before marriage, so that the individual would be in a position to inform a possible spouse of the problem and its implications. An entirely satisfactory solution, however, must await the discovery of effective treatments for these disorders and/or reliable preclinical and prenatal diagnostic tests.

Of course, it is important to realise that through a genetic Register system, relatives who prove to be at low risk can be reassured and anxieties, which often exist in such family members, can be dispelled.

Attitudes to the acceptability of genetic Registers will not only vary from disorder to disorder, but will also depend on the amount of support, both voluntary and statutory, which individuals may have experienced. The family doctor may be able to play a major part in the support of families involved with genetic disorders. Wilkie and Sinclair (1977) found that over 95% of family doctors in the south-east of Scotland were in favour of a genetic Register, but whenever possible they felt they would like to be involved in the counselling and follow-up support, though they looked to the geneticist for information about diagnosis and risks.

ACCEPTABILITY TO THE FAMILY DOCTOR

A very important problem with any genetic Register system is its acceptability to family doctors. An important function of the family doctor, in the light of his intimate knowledge of the family situation, is to augment the information given to a patient by the geneticist, and to ensure that continuing support for the patient and his family is available when required (World Health Organization, 1969). Satisfactory care may involve a continuous exchange of information, on the patient's behalf, with non-genetic specialists and with a variety of non-medical agencies. These may include the DHSS (for example, invalidity allowance), educational and housing authorities, and telephone services. In this dissemination of information, there are a number of constraints imposed upon the attitude of the family doctor by the nature of genetic disease. They include concern for confidentiality, invasion of privacy, and the patient's loss of self-esteem. These matters were considered in detail.

It should be emphasised that the family doctor might reasonably be expected to play an important role in the operation of any genetic Register. Because of his often intimate knowledge of the family situation, he is not only in the best situation to protect his patients from any possible unnecessary intrusion, but in many situations he may well be able to give genetic counselling himself, and certainly provide support and help for those found to be at high risk.

Genetic Registers: national or regional?

Advantages and disadvantages exist for both national and regional genetic Registers, and the balance is likely to depend both on the disorder being considered and the aims of a particular Register.

The advantages of a national Register include the increased amount of data compared with that recorded by a local Register. This may make registration of a very rare disorder worthwhile, and may provide sufficient data on a less rare disorder to permit meaningful epidemiological analysis. A national Register also allows standardisation of data collection over the whole country, overcomes the increasing problem of geographical dispersal of relatives, and facilitates adequate staffing and funding from central sources without unnecessary duplication. However, disadvantages include the difficulties of ensuring that data are complete and accurate. A lack of personal knowledge of the families registered by those running a national Register is a particularly important factor, as well as the increased difficulties of trying to maintain confidentiality and restriction of access to valid users. This could well reduce the co-operation of families who might otherwise be willing to be included on a more local Register.

Taking into account these various considerations, it would seem probable that, at least in Britain, a national Register of genetic disorders in general is likely to be undesirable, and that the national level is also not suitable for Registers for specific genetic disorders, the aim of which is the identification and recall of individuals at risk. A national Register could, however, be appropriate for certain rare disorders for which information would be too limited at a local level, and where the aim is primarily to study the natural history and management over a prolonged period, but such Registers would be the exception.

Use of computers for genetic Registers

Computerisation of data in a genetic Register becomes important for ease of storage and retrieval when large numbers are involved, but otherwise a manual system can be quite adequate. There are, however, several other advantages of using a computer. When appropriate safeguards have been incorporated into the system, it helps maintain and enhance confidentiality. It also provides a facility for including other functions, such as programs for risk calculation (Smith, 1972; Conneally and Heuch, 1974).

With regard to computer specifications, these will depend largely on the size of the population to be covered. For a population of a million, it might be expected that 10 000 (that is, about 1%) would be an

upper limit to the number of individuals (patients and relatives) who might be included on a genetic Register. With RAPID, each individual has a total record of about 500 characters and, therefore, on this basis a Register of 10 000 would take up to 5 million characters. This is equivalent to about 2 RK05 on a PDP 11 and in current terms is not excessive. With regard to the amount of core store required, this is more difficult to estimate, as it will depend on the operating system and the computer language chosen, but 16 K words would be a minimum. Clearly with more core available, the programmer's task will be easier.

Another problem to be considered is the form that data input and output should take. With regard to input, a key system is probably the most practical, and since a written record is often required, some form of data printout might well be preferred.

Finally, there is the type of computer facility to be considered. There are a number of distinct advantages associated with a small dedicated computer actually located in the department of the main users, as opposed to a terminal associated with a large central computer. These advantages include increased confidentiality (prevention of unauthorised use and better physical security) and facility of operation (availability of interactive mode and immediate access for designated users).

Whatever system is chosen, there would be obvious advantages in using a standard form for recording data and an agreed system for coding individual items of information, such as diagnosis. This would help facilitate the exchange of data between different groups, and might hopefully lead to a standard method of data storage in the computer file. In some circumstances, it may even be possible for several groups to use the same program and hence reduce development costs. Unfortunately, there is as yet no generally agreed classification of disease which would be of specific value in a genetic Register. The 'International Classification of Disease' is not sufficiently detailed in regard to genetic syndromes and disorders. The 'Cardiff Diagnostic Classification', produced by the British Paediatric Association, has the advantage of being more discriminating in the case of certain genetic disorders because of the addition of a 5th and sometimes a 6th digit. However, an important disadvantage is that ICD codes are not always adhered to. The coding system of genetic disorders given by McKusick (1975) is useful, but unfortunately does not include multifactorial or chromosomal disorders.

A suggested coding, based on the 'International Classification of Disease' to which a 6th digit has been added to accommodate increasing heterogeneity within particular disease entities, has been devised and employed in the RAPID system. This coding system accommodates various unifactorial, multifactorial

and chromosomal disorders, and details are available on request¹.

Finally, but most importantly, consideration has to be given to data security. This can be achieved in several ways. Firstly, by encoding data which might identify individuals in the Register. Secondly, if the data are stored on disk or cassette, these should be removed from the machine and locked away when not in use. Thirdly, the system should be so designed that the data can always be recovered, even in the event of a computer malfunction, by having back up copies of the data which are stored securely.

Recommendations

As a result of their deliberations and consideration of the evidence, the Working Party proposed the following recommendations:

(1) Registers should be set up for the express purpose of tracing, following-up, and counselling individuals who are at high risk (greater than 1 in 10) of transmitting a serious genetic disorder to their offspring. The object is to ensure that such individuals are informed of the risks and the various options available to them.

(2) Registers should be organised on a regional rather than a national basis, and should be located in a regional genetics centre. When Registers already exist in Units dealing with specific genetic disorders, such as haemophilia, close liaison should be encouraged with the regional genetics centre in order to provide comprehensive facilities for counselling, including risk estimation.

(3) No individuals should be included on the Register without their full knowledge and approval.

(4) The involvement of family doctors should be sought in every case and encouraged at all stages of contacting, counselling, and follow-up of individuals at risk.

(5) The complexity of the data and the need for co-operation between centres requires a standard form for recording data and an agreed system for coding disease entities. The latter should accommodate chromosomal, multifactorial, and unifactorial disorders and should be sufficiently flexible to include newly recognised genetic disorders and possible heterogeneity.

(6) Computerisation of data in a genetic Register is recommended for several reasons. It becomes important for ease of storage and retrieval of data (including patient recall) when large numbers are involved. It has the advantage that, when appropriate safeguards are incorporated, it helps to maintain strict confi-

dentiality. It also provides a facility for fulfilling other functions such as complex risk calculations.

(7) The preferred computer system for a genetic Register requires a dedicated mini-computer located in the genetic centre. The most important advantages are increased confidentiality and facility of operation. A less satisfactory alternative is a terminal associated with a large central computer.

(8) There should be standardisation of computer equipment and computer programs, both for economic reasons and to facilitate collaboration between different genetic centres. Therefore, it is essential to co-ordinate developments in this field.

(9) The computer program, like all other aspects of the genetic Register system, must incorporate strict safeguards for confidentiality.

(10) Access to data in the Register must be restricted to certain clearly specified individuals. Personal and medical information should be released only by the clinician in charge of the Register.

(11) In establishing a regional genetic Register, provision must be made for adequate supporting staff, which might reasonably include a medical geneticist, a clerk/computer operator, and a field worker.

(12) Where a general genetic Register is not immediately feasible for economic or other reasons, a limited Register should be established for specific genetic disorders of particular importance.

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