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The NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC), based at the University of Southampton, manages evaluation research programmes and activities for the NIHR

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PROTOCOL(revised)

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

The cost-effectiveness of next generation sequencing compared with traditional genetic testing for the diagnosis of learning disabilities in children

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UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

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Abbreviations

Array CHG	Array Comparative Genomic Hybridisation
DNA	Deoxyribonucleic acid
HTA	Health Technology Assessment
IQ	Intelligence Quotient
LR*i*G	Liverpool Reviews and Implementation Group
NGS	Next Generation Sequencing
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute for Health Research
PSSRU	Personal Social Services Research Unit
RAG	Research Advisory Group
SWAN	Syndromes Without A Name
TAR	Technology Assessment Review
UKGTN	UK Genetic Testing Network
YHEC	York Health Economics Consortium

1 TITLE OF PROJECT

The cost-effectiveness of next generation sequencing compared with traditional genetic testing for the diagnosis of learning disabilities in children

2 TAR TEAM AND PROJECT 'LEAD'

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3 PLAIN ENGLISH SUMMARY

This document provides a protocol for a project to assess whether a pathway based on next generation sequencing (NGS) is more cost-effective than current approaches to genetic diagnosis for children with learning disabilities.

Genetic testing can be used to diagnose or rule out a specific genetic condition. Accurate diagnosis using conventional genetic tests can be difficult as genetic disorders that are caused by abnormalities in one gene are limited. Next generation sequencing is a new approach which allows the simultaneous study of multiple genes and its use is expected to increase the number of conditions that can be identified. It is currently being used for research purposes in a few centres in England and Wales but it has not yet been used in clinical practice to diagnose learning disabilities.

The objectives of this project are to:

- Describe current pathways that involve the use of genetic testing;
- Collect stakeholder views on the changes in service provision that would need to be put in place before NGS could be used in clinical practice;
- Describe the new systems and safeguards that would need to be put in place before NGS could be used in clinical practice;
- Explore the cost-effectiveness of using NGS compared with conventional genetic testing.

The most conservative assumption is that conventional genetic testing and NGS deliver the same outcome and, under this assumption, cost-effectiveness will be assessed by comparing the costs of the different diagnostic pathways. However, this approach does not take into account the added benefits and other aspects which may be associated with NGS. These include:

- The potential for a diagnosis to be made more rapidly;
- The provision of information on the risk of developing a condition in later life;
- Data storage and data protection issues.

Another important issue to consider is the value that the individual and their family put on having a diagnosis. Also of importance is the extent to which having a diagnosis will change clinical practice. Such aspects will be explored through a literature search and through consultation with stakeholders. This information will be used to assess the value for money of NGS compared with conventional genetic testing in the diagnosis of learning disabilities in children.

4 INTRODUCTION

Genetic testing allows the accurate diagnosis of genetic disorders, along with disease prediction, carrier testing and screening. The term 'genetic test' is used to describe a particular genetic variant (or set of variants) associated with a particular disease and the test, therefore, relies on prior knowledge of the causal mutation.[1] The 2012 *NHS Directory of Genetic Testing*[2] reports that UK genetic testing network laboratories offer tests for 519 diseases and that new tests for 48 diseases are currently being set up as NHS service. The number of tests available is rising year on year as new gene-disease associations are identified.

Array Comparative Genomic Hybridisation (array CGH) is recognised as a rapidly emerging technology capable of replacing standard diagnostic methodologies and enhancing NHS diagnostic services.[5] In order to facilitate the implementation of array CGH technology for genetic testing of learning disabilities into the NHS, the UK Genetic Testing Network (UKGTN) invited specialised services commissioners and directors of NHS cytogenetic laboratories to an expert workshop in November 2009. There was universal agreement amongst attendees that the evidence base for the use of array CGH as a first-line test (i.e. replacing traditional karyotyping methodologies) in learning disabilities was sound, robust and conclusive.[5] However, this approach can miss certain chromosomal abnormalities. Also, its ability to detect new variations of unknown significance can generate a large quantity of false positive results.[6] Nevertheless, Regier et al[7] have found it to be cost-effective for diagnosing intellectual disabilities when used instead of conventional karyotyping.

Next generation sequencing allows the simultaneous testing of all genes (from a standard venous blood sample). It can be used in three different ways:

- Targeted sequencing – sequencing of pre-identified genes (for example, the set of genes known to be associated with learning disabilities);
- Whole exome sequencing – sequencing of all genes;
- Whole genome sequencing – sequencing of all genes and also the DNA between genes.

Next generation sequencing has the potential to facilitate a rapid diagnosis. However, it is currently only being used in research to diagnose learning disabilities and the best way to use it in practice has not yet been identified.

The National Institute for Health Research (NIHR) has issued a commissioning brief for research to assess if, when diagnosing learning disabilities in children, a pathway based on NGS is more cost-effective than current genetic approaches. This document describes the protocol for such research and is being submitted for consideration as a part of LRiG's current Technology Assessment Review (TAR) research contract.

5 BACKGROUND

Learning disability is a serious and lifelong condition characterised by the impairment of cognitive and adaptive skills. It may be caused by genetic, environmental, infectious or perinatal factors. A definitive cause cannot be identified for up to half of all cases.[8] However, it is not clear how many of the cases with unidentified causes are linked to genetic rather than other factors. A 2003 paper reports that chromosomal abnormalities were present, on average, in 16.1% of individuals with learning disabilities (range 4.0-34.1%).[9]

5.1 Definition of patient group

Valuing People,[10] the 2001 White Paper on the health and social care of people with learning disabilities, included the following definition:

'*Learning disability includes the presence of:*

- *a significantly reduced ability to understand new or complex information, to learn new skills (impaired intelligence), with;*
- *a reduced ability to cope independently (impaired social functioning);*
- *which started before adulthood, with a lasting effect on development.'*

This definition is broadly consistent with that used in the current version of the World Health Organization's *International Classification of Disease (ICD-10).*[11,12] It is also in line with definitions provided in both the current and development editions of the *Diagnostic and Manual for Mental Disorders (DSM-IV and DSM-V),* although DSM-IV also categorises disabilities using intelligence quotient (IQ) (see

Table 1).[13]

Table 1 DSM-IV Learning disabilities categories

Category	IQ Score†
Mild	50-55
Moderate	30-40 to 50-55
Severe	20-25 to 35-40
Profound	<20 or 25

†There is some overlap between coding categories

An IQ score does not capture a person's strengths and abilities[14] and so provides very little information on the kind of help and support the individual might need. Furthermore, measurements of IQ can vary during a person's growth and development.

5.1.1 Terminology

There is some ambiguity in relation to the terms 'learning disabilities' and 'learning difficulties'. The Royal College of Psychiatrists[15] consider that:

> *'A person with* specific learning difficulties *will have difficulties in one or two areas of their learning, but manages well in other areas of their development. Specific learning difficulties include dyslexia (reading), dyscalculia (maths), dysgraphia (writing), dyspraxia (motor skills) and aphasia/dysphasia (language).*
>
> *A child with a* general learning disability *finds it more difficult to learn, understand and do things compared with other children of the same age.'*

Mir et al[16] explain that the term 'learning difficulties' is the preferred term amongst user organisations and disability writers, whilst 'learning disabilities' is generally used by service organisations. Key Department of Health Reports[10,17] use the term 'learning disability' rather than 'learning difficulty' to avoid confusion with educational problems.[17] This project will follow the approach taken by the Department of Health.

To add further ambiguity a number of other terms are used synonymously with, or include the definition of, learning disability. These include mental retardation (commonly used in the USA, but considered offensive in this country), mental handicap, intellectual disability, cognitive impairment, general or developmental disability, and learning disabled.

5.2 Prevalence

Attempts have been made to determine the number of children with disabilities, including learning disabilities; however, these have had limited success.[18,19] The Department of Health[17] suggests that around 2.5% of the UK population has a learning disability. Emerson and Hatton[20] used two different approaches to estimate prevalence in England. The first involved extrapolating from a sub-set of locally-held learning disability 'registers', whilst the second made adjustments to the 'register' figures which took into account the fact that these figures are likely to only include those with severe learning disabilities. Prevalence figures by age group are presented in Table 2 and estimated numbers of children with learning disabilities, calculated using Office for National Statistics Sub-national population projections are displayed in Table 3.[21]

Table 2 Estimated learning disabilities prevalence rates in England

Age	Estimated Administrative Prevalence (%)[20]			Estimated True Prevalence (%)[20]		
	Male	Female	Total	Male	Female	Total
0 – 4	0.19	0.11	0.15	0.19	0.11	0.15
5 – 9	0.61	0.32	0.47	1.21	0.72	0.97
10 – 14	0.66	0.33	0.50	2.76	1.73	2.26
15 - 19	0.82	0.50	0.67	3.22	2.10	2.67

Table 3 Estimated numbers of children with learning disabilities in England

Age	Department of Health	Emerson – 'Administrative'	Emerson – 'True'
0 – 4	85,230	5,114	5,114
5 – 9	76,786	14,436	29,793
10 – 14	74,891	14,978	67,701
15 - 19	82,423	22,089	88,028
Total	**319,329**	**56,617**	**190,636**

5.3 Diagnosis of learning disability

The first step in the diagnostic pathway occurs after someone (perhaps a professional, relative or friend) believes that a child may have a disabling condition or additional health needs. This concern may arise as part of a formal screening or surveillance programme. It could occur pre-birth if, for example, amniocentesis has shown possible Downs Syndrome; at birth for a condition with physical abnormalities; later during a consultation with a clinician for an unrelated purpose; or, in the case of less profound developmental delay, when the child starts school.

A paediatrician generally carries out the assessment of learning disabilities. The paediatrician will take a medical history as well as record physical measurements and assess the child's developmental progress. Other health professionals may be involved in the assessment, for example referral for vision or hearing assessment or to a neurologist.[22]

If the paediatrician suspects that the child's condition may be linked to a genetic abnormality the child will be referred to a regionally-based NHS clinical genetic service. The genetic service can use a number of diagnostic tools, including:[23]

- Family history taking;
- Information gathering;
- Medical history and examination;
- Clinical investigation;
- Genetic testing.

Results from a genetic test can generally be produced within 4 months. Some NHS centres offer a turn-around time of 6 weeks for specific tests. Certain specialised tests can only be carried out abroad.

The clinical genetic service provides genetic counselling. The extent of counselling will depend on the result of the genetic test. Sometimes it will only be appropriate to counsel parents, but in other cases the wider family may need counselling and, perhaps, also testing. For example, if both parents are found to be carriers (i.e. each parent has one "normal" and one defective gene) then siblings could also be silent carriers of the condition. Even if the siblings do not have the condition themselves, they could potentially pass the mutated gene to their children.

5.4 The value of a diagnosis

In 1995 the American College of Medical Genetics sponsored a conference in Minnesota, USA. The purpose of the conference was to use available literature and expert opinion to produce consensus recommendations on the evaluation of mental retardation. The benefits of a genetic evaluation, as identified at the conference, are displayed in Table 4[8].

Table 4 Benefits of genetic evaluation

For the individual patient	For parents
Identification of appropriate medical and non-medical therapies	Anticipatory guidance
Identification of indicated medical/intervention/referrals	Education and advocacy
Presymptomatic screening for associated complications/functional disabilities	Referral to appropriate medical and social service agencies
Educational planning	Referral to support groups
Elimination of unnecessary testing and evaluations	Reproductive counselling, carrier testing, prenatal diagnosis
	Family networking

In the UK, as part of a larger study looking at the implications of whole genome sequencing health,[24] Gogarty used feedback from interviews (38 participants), a forum (46 registered and discussion groups (36 people) to develop recommendations for service change to the investigation of children with developmental delay. Participants included parents, patients, and representatives from voluntary organisations. As part of the consultation exercise asked to describe some of the advantages and disadvantages of genetic testing for learning Some of the most common responses are displayed in

Table 5.[25]

Table 5 Parents' views on the advantages and disadvantages of genetic testing for learning disability

Advantages	Disadvantages
May provide a name for what is wrong	There might not be a diagnosis
Can help put you in contact with a supportive community	There might not be a community to connect to if the disorder is very rare
May help you find out more about the disorder	There might not be any recognised medical treatment regime for the named condition
Other family members can be tested to see if they are affected	It may cause stress for your immediate and wider family
Can help long-term planning for your child's and family's future	It could impact on relationships with the extended family
Can alleviate concerns that developmental delays are the parents' or family's fault	It may make the future look more bleak
Can mean that others become more sympathetic/supportive	Having a named condition can sometimes result in negative stereotypes and labels
You may be able to access more/improved services	It may cause problems with securing insurance cover
It can allow parents to find a degree of 'closure'	In a worse-case scenario it may impact on medical services

5.5 The aim and objectives of the HTA project

The aim of this project is to find out whether a diagnostic pathway based on NGS might be more cost-effective than current approaches to genetic testing diagnosis for children with learning disabilities.

The objectives of the project are to:

- Describe current pathways that involve the use of genetic testing;
- Collect stakeholder views on the changes in service provision that would need to be put in place before NGS could be used in clinical practice;
- Describe the new systems and safeguards that would need to be put in place before NGS could be used in clinical practice;
- Explore the cost-effectiveness of using NGS compared with conventional genetic testing.

6 METHODS

6.1 Overview

Drummond et al[26] have argued that although the general methods for economic evaluation are well developed, several methodological challenges arise when diagnostic devices (such as, for example, NGS for genetic testing) are evaluated. The challenges identified by Drummond et al[26] include:

- The value of improved diagnosis cannot be separated from the value of the improvement in patient outcome resulting from the subsequent treatment;
- Diagnostic technologies often have multiple applications and the overall value of the device could be considered as a weighted average of its multiple uses;
- There is a 'learning curve' associated with the use of the device and the efficacy of the device depends not only on the device itself but how it is used;
- Wider economic implications (for example, training and/or local organisation adjustments) may be required to harness the improved cost-effectiveness;
- Equivalent clinical evidence may not be available for all comparators;
- Prices are likely to change over time because of the market entry of new products, or because of the ways in which procurement takes place.

This project will collect data and information to allow 'value for money' to be assessed, where:[27]

> *'Good value for money is the optimal use of resources to achieve the intended outcomes.'*

The assessment will be based on the analytical framework set out by the National Audit Office,[27] namely:

1. Establishing what is optimal;
2. Capturing the scale of resources (for example, staff costs, consumables, funding streams);
3. Identifying expected and actual outcomes (for example, increased number of diagnoses, decreased time to diagnosis, quality of service, adverse, perverse or unintended consequences);
4. Establishing the consequences of the identified performance for value for money (i.e. were the outcomes achieved worth it given, for example, the cost, the effort involved);
5. Drawing an overall conclusion (i.e. comparison with conventional genetic testing);
6. Making recommendations (for example, improve process and practices, reduce costs, raise awareness of benefits).

The information required to carry out the assessment will be collected via:

- Targeted literature searches;
- Consultation with stakeholders; and a
- Workshop.

The way in which these elements inform the cost-effectiveness analysis is shown in Figure 1.

Following completion of the interviews an influence diagram will be developed. This will show how different elements of the diagnostic process are linked. The influence diagram will be verified for face validity by clinical experts (members of the Research Advisory Group (see section 6.1.1)) before the economic assessment is finalised.

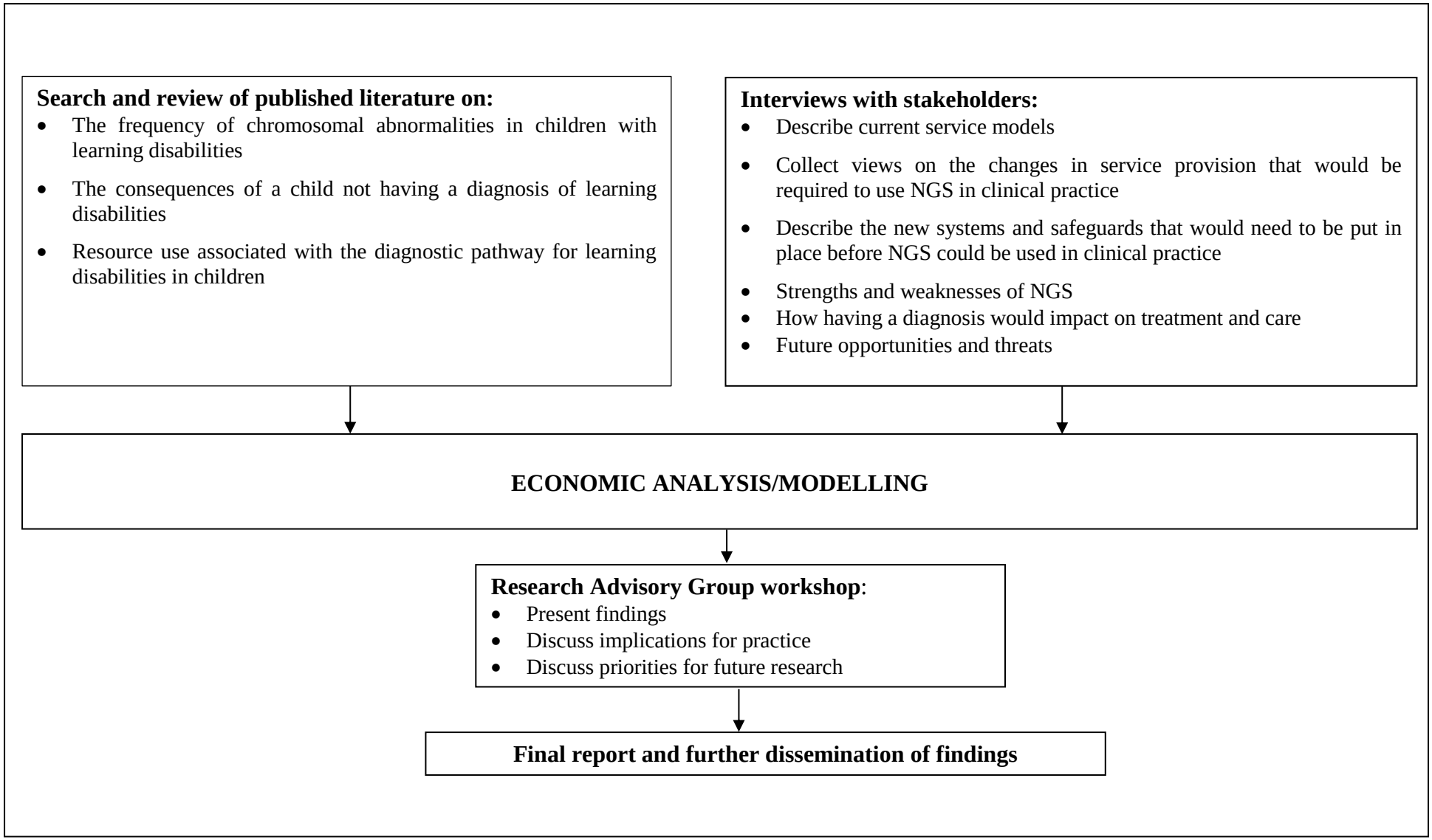
6.1.1 Research Advisory Group

A Research Advisory Group (RAG) has been established to help shape the direction of the research. A list of members may be found in Table 6. This group will be invited to comment on the draft data collection tools. The group will also be invited to attend an end of project workshop, the purpose of which will be to share findings and discuss implications for practice and priorities for future research. In addition, group members will also be asked to make themselves available from time to time to respond to ad hoc queries by email.

Table 6 RAG members

Organisation/expertise	Details
NHS Commissioning Board and/or Department of Health	Awaiting response from one individual who is based at the Department of Health and from another who has recently joined the NHS Commissioning Board.
Clinical geneticist	**Professor Jill Clayton-Smith** – Clinical Geneticist (NHS CMFT) with an extensive background of research relating to genetic disorders in children. Current research interests involve examining the use of newer genetic technologies, particularly NGS for the diagnosis of developmental disorders and intellectual disability.
Genetic counsellor	**Dr Laura Boyes** is the Principal Genetic Counsellor at Birmingham Women's Hospital NHS FT. Laura has a PhD in molecular genetics alongside molecular and psychosocial research experience in genetics. She is also a member of the Association of Genetic Nurses and Counsellors (AGNC) committee.
Bio-information specialist	**Sanjeev Bhaskar** is the Lead Bioinformatician at NHS CMFT who leads the development of NGS analysis pipelines for diagnostics.
Representatives from a testing centre	**Dr Simon Ramsden** – Consultant Clinical Scientist at NHS CMFT who has been delivering traditional genetic services for learning disabilities for a number of years.
	James O'Sullivan – Clinical Molecular Geneticist who leads the NHS CMFT next generation sequencing team.
Paediatricians	**Dr Megan Thomas** - Consultant Community Pediatrician at Blenheim House Child Development and Family Support Centre. She has a background in genetics and a PhD in a learning disability topic.
	Dr Imelda Hughes – Consultant Paediatric Neurologist (NHS CMFT).
GP	**Dr Matt Hoghton** is the RCGP clinical champion for learning disabilities and a GP in Clevedon, Somerset.
SWAN	**Dr Alistair Kent** - Director of Genetic Alliance UK SWAN (Syndromes Without A Name) is a project run by Genetic Alliance UK offering support and information to families of children with undiagnosed genetic conditions. Alastair is a member of a number of local, national and European genetics related committees.
BACD	**Dr Karen Horridge** is a disability paediatrician in Sunderland. She is chair of the North of England Collaborative Cerebral Palsy Survey, part of the North East's learning disability clinical network and, from 25 March 2013, will be chair of the British Academy of Childhood Disability (BACD). She has established regular joint clinics with colleagues from Clinical Genetics in a number of districts as she recognises the importance of timely genetic diagnosis to inform health care planning. As well as representing the BACD Karen will be reporting back to Karen Turner at the Department of Health
UNIQUE	**Dr Sarah Wynn** - Information Officer UNIQUE is a source of information and support to families and individuals affected by any rare chromosome disorder and to the professionals who work with them. Sarah is currently preparing a family-friendly guide on NGS. She has hands on sequencing experience through many years' research work at the University of Hong Kong and for the MRC. She also has experience of talking to families about their children's diagnostic pathways.
Individual with expertise in ethics and genetics	**Professor Anneke Lucassen** is a clinical geneticist and academic who leads an interdisciplinary programme of research into the social, ethical and legal aspects of developments in genetics. She is cofounder of the UK Genethics Group which is a national forum for the exploration of ethico-legal issues arising in genetic practice. She sits on the Nuffield Council of Bioethics and is currently on its working party exploring ethical issues in genomics and data linkage.

Figure 1 Diagram showing how the key research tools are linked



6.2 Project elements

The project will comprise five main elements:

1. Search and review of published literature on:
    - The number of children with learning disabilities of unknown cause;
    - The consequences of not having a diagnosis of learning disabilities;
    - Resource use associated with the diagnostic pathway for learning disabilities in children.
2. Interviews with key stakeholders;
3. Assessment of cost-effectiveness;
4. Workshop (to share findings and discuss implications for practice and priorities for future research);
5. Final reporting.

6.2.1 Literature search

A systematic review will not be carried out. The primary purpose of the searching exercise is to identify data and information that will inform the economic analysis. Each search will be targeted on a particular question, including:

- The number of children with learning disabilities of unknown cause;
- The consequences (for individuals, their carers and the NHS) of not having a diagnosis;
- Resource use relating to genetic diagnosis (conventional testing and NGS), for example, time and costs.

Other targeted searches will be carried out if information collected via the interviews highlight specific needs, for example, if further details (or values) are required to allow us to carry out the cost-effectiveness analysis.

Diagnosis using genetic techniques is a rapidly evolving area of medicine and therefore searches will be restricted to studies published from 2000 onwards. Papers will be identified by searching key databases which include papers on clinical effectiveness and cost-effectiveness, namely:

- Cochrane Library;
- MEDLINE;
- EMBASE;
- PsycINFO;
- Health Management Information Consortium (HMIC);
- Cumulative Index to Nursing and Allied Health Literature (CINAHL);
- EconLit;
- Education Resources Information Center (ERIC).

Search terms for identified questions will be combined with:

- Learning dif*;
- Learning dis*;
- Intellectual disability*;
- Mental retardation;
- Mental handicap;
- Global developmental delay.

Autism will also be included as a search term as its use may reveal some additional relevant items (i.e. those relating to autism *and* learning disabilities).

Only studies published in English will be identified. Before acquiring papers, preliminary screening of the literature highlighted by the search will be carried out to discard irrelevant material. Initially, titles and abstracts be scanned by two researchers and studies that are clearly irrelevant will be removed. The remaining abstracts will be scrutinised in relation to the required data and those papers that do not deal directly with the data gaps will be excluded. Once this sifting process has been completed, paper copies of the selected studies or reviews will be acquired.

The stakeholder interviews will be used to help identify any other relevant published studies or grey literature (including data) of relevance to the economic analysis.

6.2.2 Stakeholder interviews

We will interview individuals with specific knowledge or responsibilities in the following areas:

- **Identification and referral of children for genetic testing**, including health visitor; Professions Allied to Medicine*; GP*; paediatrician*; clinical geneticist.
- **Genetic testing**:
    - Clinical criteria for deciding whether or not to employ NGS;
    - Initial assessment;
    - Carrying out tests;
    - Analysis of test results (bioinformatician);
    - Data storage;
    - Data protection;
    - Genetic counselling;
    - Changing from a research approach into clinical practice.
- **Provision of health care pre-diagnosis, post-diagnosis**, including: Professions Allied to Medicine*; learning disabilities specialist nurse; community children's nursing team; GP*; paediatrician*.
- **Others**, including specialist commissioner; voluntary sector support groups; ethics and psychological issues, and representatives from social care and education.

*Identified individuals will be asked questions relating to both areas.

The purpose of the interviews is to:

- Gather information on current service models;
- Collect views on the changes in service provision that would be required to use NGS in clinical practice;
- Describe the new systems and safeguards that would need to be put in place before NGS could be used in clinical practice.

We will also collect views on:

- The strengths and weaknesses of NGS;
- How having a diagnosis would impact on treatment and care;
- Ethical issues;
- Future opportunities and threats.

This list is not necessarily comprehensive. It is possible that it will expand if interviewees suggest colleagues who they feel have important knowledge or views. In a scoping exercise such as this identification of individuals is necessarily pragmatic. In effect, a 'snowballing' approach will be employed. A number of key individuals have been identified through their recent publications or information about their work posted on the internet. We will initially arrange interviews with these individuals and ask them to suggest colleagues with expertise or experience which will inform this project. Such an approach, although necessarily biased towards those with an interest in this area, will prevent unnecessary time being expended trying to set up interviews with individuals who have little to contribute.

To help ensure that anyone who wishes to contribute to the project is able to do so we will send an email to the British Society for Human Genetics[a] asking them to circulate brief information about the project (for example, on their website or via a newsletter). The information will include the contact details of a named member of the research team so that anyone who wishes to set up a time for an interview, or anyone who would like to send us information (for example, grey literature), is able to do so.

Interviews will be tailored to reflect the knowledge and specialist area of each interviewee. A list of possible discussion topics will be sent to the interviewee prior to interview. We propose to undertake about 30 – 40 (maximum 50) semi-structured interviews. The majority of the interviews will be

[a] The BSHG is an independent body representing UK human genetics professionals. Its constituent organisations are: Clinical Genetics Society; Association for Clinical Cytogenetics; Clinical Molecular Genetics Society; association of Genetic Nurses and Counsellors; Cancer Genetics Group; and Society for Genomics, Policy and Population.

undertaken on a one-to-one basis by telephone, although some interviews will be undertaken face-to-face (either individually or in small groups). All interviews will be recorded. The recordings will not be transcribed verbatim but will be used as an *aide memoir* to help recall specific details that were raised during the interview. We will e-mail a summary of the key points raised during the interview to the interviewees and offer them the opportunity to check the notes for accuracy and add any additional points that may have occurred to them after the interview has ended.

Key themes from the interviews will be identified and collected; information will be summarised by theme. Any information which does not have a direct bearing on costs or effectiveness will be either summarised in the main report or included as an appendix, depending on importance.

6.2.3 Economic modelling

As described in section 6.1, the economic assessment will be based on the analytical framework set out by the National Audit Office.[27] The extent of the economic analysis will depend on the availability of data. As NGS is only currently being used in research, the costs that we develop for its inclusion into a diagnostic pathway may only be considered as indicative.

The economic assessment will adhere to a number of key principles:

- All assumptions will be clearly identified and a critical appraisal of their strengths and weaknesses presented in the report;
- Appropriate sensitivity analyses will be carried out to assess the robustness of results to realistic variations in underlying parameter values and key assumptions;
- Where it is not possible to quantify a particular factor we will explore the use of proxies that are quantifiable;
- Costs will, wherever possible, be extracted from national sources (e.g. PSSRU, NHS reference costs) or, if not available, published papers or reports.
- The time horizon will be up until the age of 18 years (i.e. childhood);
- Costs and outcomes will be discounted at 3.5% in line with the National Institute for Health and Clinical Excellence (NICE) reference case.[28]

6.2.4 Workshop

All members of the RAG will be invited to attend a full day workshop in Liverpool. The purposes of this workshop will be to:

- Share findings from the draft report, giving attendees the opportunity to provide comments and suggestions before the report is finalised;
- Discuss implications for future practice;
- Discuss priorities and opportunities for future research.

6.2.5 Final reporting

Following the workshop the draft report will be finalised before being circulated by the NIHR for peer review. The feedback from peer review will be taken on board to produce the final report. The final report will be published by the NIHR as an HTA monograph. In addition, LR*i*G has a policy of publishing project findings in other appropriate journals and at conferences.

7 EXPERTISE IN THIS TAR TEAM AND COMPETING INTERESTS

The Liverpool Reviews and Implementation Group was established at the University of Liverpool in April 2001. It is a multi-disciplinary research group whose purpose, in the first instance, is to conduct TARs commissioned by the HTA programme. The team has substantial expertise in literature searching, systematic reviewing, assessing clinical outcomes, economic modelling and health economics, and is well practised in applying this expertise to health technology evaluations. In addition, various members of the team have been involved in recent projects focusing on the use of genetic testing for diagnostic purposes as well as projects considering the needs of people with learning disabilities.

A subset of the LR*i*G team, none of whom have any competing interests, has been selected to work on this project on the basis of their specific expertise. In addition, a clinical geneticist and a paediatrician are also included as part of the core team. The expertise of the clinicians will complement the evaluation skills of other members of the research team. It will be especially valuable when interpreting some of the subtleties and nuances that will emerge during the course of the project. In particular, the team will benefit from the clinicians' specific knowledge and experience in:

- Working with children with learning disabilities and their families;
- Working as part of a team of NHS professionals;
- Knowledge of genetics (including recent developments in the field).

The team will work closely, communicating at least weekly via telephone and/or email. Due to the clinical commitments and geographical locations of team members face-to-face meetings will be scheduled on a monthly basis.

An overview of each individual's relevant skills and experience is provided below, with their expected contributions to the project summarised in

Table 7.

Sophie Beale is a Research Associate who has been employed by LR*i*G for 15 months. Prior to joining LR*i*G she worked at York Health Economics Consortium (YHEC) at the University of York for 11 years. She has considerable experience of undertaking service reviews and qualitative and quantitative evaluations in a range of treatment areas for pharmaceutical, NHS and local and national government clients. Many of her projects have involved interviewing managers, front-line staff, users, carers and other key stakeholders. Furthermore, she has considerable experience of project management, data analysis, economic modelling, facilitating focus groups, designing data capture tools, information synthesis and report writing, all of which are relevant to this project.

Sophie was involved in a HTA project which explored the economic evaluation of the clinical and cost-effectiveness of testing for cytochrome P450 polymorphisms in patients with schizophrenia treated with antipsychotics. She also led the design of the data collection tools for the economic evaluation carried out as part of the Big Study for life-limited children and their families. Furthermore, she has worked successfully with Diana Sanderson on several projects, including a needs assessment for people with learning disabilities and a study to assess the economic impact of family support teams for children with life-limiting conditions.[b]

Diana Sanderson has worked as a self-employed Independent Health Economist (trading as Mill Mount Consulting) for almost 10 years. Prior to this she worked as a Senior Research Fellow at York Health Economics Consortium at the University of York for 16 years, and retains her links with the organisation as an Associate Senior Consultant. Before joining YHEC, she had been a Lecturer in Economics at the University of Durham for several years. She therefore has over 25 years of experience working directly on research and consultancy projects for clients from health and social care, often focusing on the economic aspects of these projects. Clients have ranged from Government Departments to NHS Trusts, Social Services Departments and voluntary organisations. She is skilled in undertaking both quantitative and qualitative analysis, including interviewing senior clinicians and managers, conducting focus groups with service users and carers, designing questionnaires, and analysing activity and financial data. Many of her projects have involved comparing the costs, benefits and cost consequences of alternative approaches to delivering a service.

[b] Further details of selected projects:
Sanderson DJ, Lowson K, **Beale SJ**, Economic Impact of the Family Support Teams (The Rainbow Trust) August 2011
Beale SJ, **Sanderson DJ**. Mental Health Needs Assessment (NHS Leeds). July 2010.
Beale SJ, **Sanderson DJ**. Learning Disabilities Needs Assessment (NHS Barnsley). June 2010
Bagust A, McLeod C, **Beale SJ**. The Cost-effectiveness of Testing for Cytochrome P450 Polymorphisms in Patients Treated with Antipsychotics (University of Liverpool for NIHR). November 2008. http://www.hta.ac.uk/fullmono/mon1403.pdf

Several recent projects have focused on mental health and/or learning disability services. As the author or co-author of over 200 reports, she is used to synthesising and presenting information in ways that meet the clients' specific requirements (e.g. a research report; a business case; an option appraisal; a service evaluation). Although currently self-employed, she often works with other organisations, including University-based research departments and independent companies.

Anna Sanniti has a BSc (Hons) in Biomedical Science (Genetics) from Brunel University and an MSc in Pharmacogenetics and Stratified Medicine from University College London; Anna has recently joined LR*i*G as a researcher with expertise in genetics. As part of her undergraduate degree she spent a year working for the Health Protection Agency on a project to enable the rapid identification of different influenza subtypes. Her knowledge of genetics, strong oral and written communication skills, as well as her experience of analysing data will be valuable assets to this project.

Dr Kay Metcalfe has been a Consultant Clinical Geneticist at St Mary's Hospital, Manchester since 2001. Her special interests include fetal medicine, cardiac genetics, dysmorphology and the genetic assessment of children with learning disability.

Dr Maria Hall (MBBS, MRCPCH) is a Specialist Registrar in Paediatrics in her penultimate year of training, undertaking Higher Specialist Training in Community Child Health. She qualified from the University of Newcastle-upon-Tyne in 2001 and gained Membership of the Royal College of Paediatrics and Child Health in 2006. She has ten years' paediatric experience, of which three years have been subspecialising in Community Child Health working in Ormskirk, Warrington, and at Alder Hey Children's Hospital. Currently she is based in Blackpool at Blenheim House Child Development and Family Support Centre where she regularly assesses and investigates children with developmental delay and learning difficulties. Whilst there she has become involved with the paediatric research team, undertaking training and participating in ongoing studies.

Dr Yenal Dundar is currently a Specialist Registrar in General Adult Psychiatry at Mersey Care NHS Trust and part-time LR*i*G systematic reviewer. He is an experienced information specialist and his role in this project will be to carry out the literature searches.

Dr Angela Boland is the Associate Director of LR*i*G and has worked at the University of Liverpool as a health economist and project co-ordinator for 17 years. Angela works across all of LR*i*G's projects and acts as proof-reader and copy-editor to improve the quality of LR*i*G's outputs.

Table 7 Contributions of team members

Team member	Contribution
Sophie Beale	Project lead who will be actively involved in all aspects of the project
Diana Sanderson	Involved in all (non-management) aspects of the project
Anna Sanniti	Provision of general project support as required including arranging the telephone interviews
Kay Metcalfe	Will work actively with LR*i*G throughout the assessment phase as part of the core team
Maria Hall	Will work actively with LR*i*G throughout the assessment phase as part of the core team
Yenal Dundar	Literature searches
Angela Boland	Quality assurance

8 APPROACH TAKEN TO RISK MANAGEMENT

The major risks for this project concern the interviews. The potential risks include a poor response rate and a delayed response. These risks are unavoidable in studies which rely on responses from the field of interest. However, we believe that these risks can be managed in several ways. The main issues, mitigating actions and recovery plans are presented in Table 7Table 8.

Table 8 Risk assessment

Issue	Likelihood of Risk (low, medium or high)	Mitigating Action(s)	Recovery Plan
Low response to invitation to interview	Low	We will attempt to encourage potential interviewees by highlighting the importance attached to this work. This will be done in an accompanying letter which will explain that the project is funded by the NIHR and that results will be published widely.	If such a case were to arise we would seek suitably qualified/experienced replacement interviewees who would be able to provide a similar contribution to this evaluation.
Unable to arrange interviews within the timeframe of the project due to prior commitments of stakeholders	Low	We have a named team member whose role includes arranging interviews.	If such a case were to arise, we would ask that individual to recommend a suitably qualified colleague who could contribute to this evaluation.
RAG respond negatively to findings	Low	RAG members will be involved in the design of the research tools and will also be interviewed. Their views will, therefore, be included in the report. Asking interviewees to review our interview notes will help ensure that we accurately portray their views	Sharing findings with the RAG at the workshop will help ensure that all views are represented appropriately.
Cover if researchers leave	Low	Research team members have been approached and confirm that they will be available for the duration of the project.	LR*i*G is made up of a pool of experienced researchers and, if necessary, it would be possible to instate a substitute team member.

9 PROJECT TIMELINES

The actual start date is dependent on the time taken to receive and respond to reviewer feedback. An indicative timetable is displayed in Table 9.

Table 9 Indicative project timetable

	Month 1				Month 2				Month 3				Month 4				Month 5				Peer Review	Month 6			
Literature review:																									
Refine search strategies and carry out searches																									
Obtain and review literature																									
Collate findings																									
Stakeholder consultation:																									
Develop and finalise interview protocols																									
Identify stakeholders and distribute invitations																									
Carry out interviews																									
Collate interview findings																									
Economic modelling																									
Other elements:																									
Workshop																									
Draft report preparation																									
Final report preparation																									

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11 APPENDICES

11.1 DSM and ICD-10 learning disabilities definitions,

DSM-IV definition

'Mental Retardation[13]:

A. Significantly subaverage intellectual functioning: an IQ of approximately 70 or below on an individually administered IQ test (for infants, a clinical judgment of significantly subaverage intellectual functioning).

B. Concurrent deficits or impairments in present adaptive functioning (i.e., the person's effectiveness in meeting the standards expected for his or her age by his or her cultural group) in at least two of the following areas: communication, selfcare, home living, social/interpersonal skills, use of community resources, self-direction, functional academic skills, work, leisure, health, and safety.

C. The onset is before age 18 years.

Code based on degree of severity reflecting level of intellectual impairment:

317 Mild Mental Retardation: *IQ level 50–55 to approximately 70*

318.0 Moderate Mental Retardation: *IQ level 35–40 to 50–55*

318.1 Severe Mental Retardation: *IQ level 20–25 to 35–40*

318,.2 Profound Mental Retardation: **IQ level below 20 or 25**

DSM-V definition[13]

DSM-V is scheduled for publication in 2012 and the proposed revision is:[13]

'Intellectual Developmental Disorder (IDD) is a disorder that includes both a current intellectual deficit and a deficit in adaptive functioning with onset during the developmental period. The following 3 criteria must be met:

A. Intellectual Developmental Disorder is characterized by deficits in general mental abilities such as reasoning, problem-solving, planning, abstract thinking, judgment, academic learning and learning from experience.

B. Impairment in adaptive functioning for the individual's age and sociocultural background. Adaptive functioning refers to how well a person meets the standards of personal independence and social responsibility in one or more aspects of daily life activities, such as communication, social participation, functioning at school or at work, or personal independence at home or in community settings. The limitations result in the need for ongoing support at school, work, or independent life.

C. All symptoms must have an onset during the developmental period.'

ICD-10 definition

'Learning disabilities is a condition of arrested or incomplete development of the mind, which is especially characterised by impairment of skills manifested during the developmental period, contributing to the overall level of intelligence, i.e. cognitive, language, motor and social abilities.'[11,12].

11.2 Genetic testing centres in England and Wales

Table 10 Genetic testing centres in England and Wales offering learning disability diagnostic services

Region	Name	Address
East Anglia	East Anglian Medical Genetics Service	East Anglian Medical Genetics Service Box 134 Level 6, Addenbrookes Treatment Centre, Addenbrooke's Hospital Cambridge CB2 0QQ
London-North Thames	North East Thames Regional Genetics Service	Clinical Genetics: Great Ormond Street NHS Trust, Level 4, Regional Molecular Genetics Laboratory Level 6, Regional Cytogenetics Laboratory Level 5 York House,37 Queen Square, London WC1N 3BH
	North West Thames Regional Genetics Service	The Kennedy Galton Centre, Northwick Park And St Mark's NHS Trust, Watford Road, Harrow HA1 3UJ
London-South Thames	South East Thames Regional Genetics Service	London Guy's Hospital Genetic Centre, Molecular (DNA) Laboratory and Cytogenetic Dept. GSTS Pathology, 5th Floor Tower Wing.
	South West Thames Regional Genetics Service	Floor 0, Jenner Wing St George's University of London, Cranmer Terrace, London SW17 0RE
Midlands	Leicestershire Genetics Centre	University Hospitals of Leicester, NHS Trust, Leicester Royal Infirmary Leicester LE1 5WW
	West Midlands Regional Genetics Service	Birmingham Women's NHS Foundation Trust, Edgbaston Birmingham B15 2TG
Northern	Northern Genetics Service	Institute of Human Genetics, International Centre for Life, Central Parkway Newcastle upon Tyne NE1 3BZ
	Yorkshire Regional Genetics Service	Yorkshire Regional Genetics Service, Department of Clinical Genetics, Ward 10, 3rd Floor, Chapel Allerton Hospital, Chapeltown Road, Leeds LS7 4SA
North West	Cheshire and Merseyside Regional Genetic Laboratory	Liverpool Women's Hospital NHS Foundation Trust, Crown Street Liverpool. L8 7SS
	Genetic Medicine, Manchester	6th Floor, St Mary's Hospital, Central Manchester University Hospital, Hospitals NHS Foundation Trust, Oxford Road Manchester. M13 9WL
Oxford	Oxford Genetics Service	Oxford University Hospitals NHS Trust, The Churchill, Old Road, Headington, Oxford OX3 7LJ
South West	South Western Regional Genetics Services	*Bristol, Bath, Somerset and Gloucestershire* St Michael's Hospital, Southwell Street, Bristol BS2 8EG
		Devon and Cornwall Clinical Genetics Department, Royal Devon & Exeter Hospital (Heavitree), Gladstone Road, Exeter EX1 2ED
Trent	Nottingham Regional Genetics Service	Nottingham University Hospital NHS Trust, City Hospital Campus, Hucknall Road, Nottingham. NG5 1PB
	Sheffield Genetic Services	Sheffield Children's NHS Foundation Trust, Western Bank, Sheffield. S10 2TH
Wales	All Wales Medical Genetics Service	Institute Of Medical Genetics, University Hospital Of Wales, Heath Park, Cardiff. CF14 4XW

Table 11 Genetic testing centres in England and Wales that do not offer learning disability diagnostic services

Region	Name	Address
London	Barts NHS Trust E1	Barts NHS Trust Molecular Pathology Suite 3rd Floor, Pathology and Pharmacy Building 80 Newark Street Whitechapel London E1 2ES (Clinical, Molecular Genetic Laboratory Service for Retinoblastoma only).
	Centre For Cardiovascular Genetics	UCL Medical School Dept Medicine, Cardiovascular Genetics The Rayne Institute University Street London. WC1E 6JJ (Molecular Genetics- Laboratory Service Only).
	Neurogenetics Centre WC1N	National Hospital for Neurology and Neurosurgery 6th Floor, Queen Square House Queen Square London WC1N 3BG (Molecular Genetics- Laboratory Service Only).
	Retinoblastoma Genetic Screening Unit E1	Barts and The London NHS Trust, Molecular Pathology Suite 3rd Floor, Pathology & Pharmacy Building 80 Newark Street, Whitechapel London E1 2ES (Clinical, Molecular Genetic Laboratory Service for Retinoblastoma only).
	South East Thames Haemato-Oncology Cytogenetics SE5	King's College Hospital, Denmark Hill, London SE5 9RS (Cancer Cytogenetics).
	The Royal Marsden NHS Trust	Academic Haematology And Cytogenetics, F Block Sutton Surrey. SM2 5PT (Cancer Cytogenetics).
	UCL Centre for Preimplantation Diagnosis (PGD)	Dept of Obstetrics & Gynaecology UCL, 86-96 Chenies Mews, London WC1E 6HX (Genetic counselling/ Clinical for PGD only)
Southampton	Wessex Clinical Genetics Service	Princess Anne Hospital Southampton. SO16 5YA (Genetic Counselling/Consultations about genetic or potentially genetic disorders)