A scoping study to explore the cost-effectiveness of next-generation sequencing compared with traditional genetic testing for the diagnosis of learning disabilities in children

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Scientific summary

Diagnosis of learning disabilities in children

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Background

Learning disability (LD) is a serious and lifelong condition characterised by the impairment of cognitive and adaptive skills. Some cases of LD with unidentified causes may be linked to genetic factors. However, the proportion of cases linked to genetic rather than other factors is not clear. A diagnosis may not only have an impact on decisions about a child's care but also may affect their wider family, for example in terms of family planning decisions. Next-generation sequencing (NGS) techniques are new approaches to genetic testing that are expected to increase the diagnostic yield for children with LDs.

Aim and objectives

The aim of this scoping study was to find out whether a diagnostic pathway based on NGS might be cost-effective compared with current approaches to genetic testing for LDs in children. The objectives of the project were 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.

Methods

Information was collected through a structured review of the literature and stakeholder interviews. A research advisory group (RAG) workshop was held towards the end of the project. The aim of the workshop was to discuss the draft report. It also provided an opportunity to discuss the implications of the findings for future practice and to identify priorities and opportunities for future research addressing the cost-effectiveness of NGS technologies.

The approach to identifying relevant studies and reports included a number of strategies. The formal scoping searches carried out at the beginning of the study identified only a few useful studies. A number of relevant published studies and reports were highlighted during the stakeholder interviews. Further studies and reports were identified through examining the references listed in the bibliographies of useful studies as well as through internet searches. To ensure that no important publications had been overlooked a comprehensive search strategy was developed during the final months of the study. This included additional search terms that had been identified as important during the course of the study. Findings from these later searches revealed that the pragmatic approaches to searching had identified almost all relevant studies.

Interviews, which were semistructured but tailored to reflect the knowledge and specialist area of each interviewee, were undertaken with 33 stakeholders. These stakeholders included doctors working with children with LDs in generic and specialist capacities in NHS primary and secondary care settings as well as genetics specialists working in laboratories, NHS clinical settings and universities. Several interviewees held academic posts and NHS positions. Other interviewees included representatives from the Department of Health and organisations working with families of children with LDs, a bioethicist and individuals with

expertise in providing professional training in biomedicine and raising public awareness of genetics and its implications. As well as their main role, many of the interviewees also sat on national-level groups and committees and therefore had a national as well as a local/regional perspective.

Findings

Pathways

Genetic testing pathways can be divided into five different types, namely karyotyping, array comparative genomic hybridisation (aCGH), targeted sequencing using gene panels, whole-exome sequencing (WES) and whole-genome sequencing (WGS). Karyotyping has been used in the NHS for many years as the first-line test in clinical practice for diagnosing LDs in children. However, this approach is being replaced in clinical practice by aCGH (unless karyotyping is specifically indicated). In terms of the use of NGS for the diagnosis of LDs, targeted gene sequencing, which involves sequencing a set of pre-identified genes, is still in its infancy in clinical practice whereas WES (sequencing of all genes) and WGS [sequencing of all genes and also the deoxyribonucleic acid (DNA) between genes] are currently being used only in research settings.

Changes in service provision

Views on the changes in service provision that would need to be put in place before NGS could be used in clinical practice were drawn from the stakeholder interviews. It is important to note that the introduction of NGS technologies in NHS clinical settings for the diagnosis of children with LDs will not occur in isolation but will be influenced by the needs of other clinical specialties using NGS. In particular, there are many data-related issues, mainly generated by the need to process, analyse and store vast amounts of data. Furthermore, there may be a need for more centralisation of the current (regional) genetics laboratories or at least some subspecialisation (i.e. some 'super laboratories') within them.

Staffing numbers and training were also considered important by some interviewees, especially regarding the need for more bioinformaticians and genetic counsellors. Limited formal qualification-bearing education and training opportunities are being developed, but these take several years of highly specialised work to complete. Furthermore, there is a significant need for genetics-related training (and/or awareness raising) for a wide range of patient-facing staff, including general practitioners and paediatricians. In addition, the general public need to be more widely educated about genetics-related issues and involved in debates and discussions about their ethical and other implications.

It was also noted that, as the number of children undergoing testing with NGS technologies increases, there will be even more pressure on organisations providing family support and information.

New systems and safeguards

New systems and safeguards will be very important. From an ethical perspective, two key (and inter-related) aspects should be considered, ideally at a national level, drawing on experience from other European countries and the USA: first, gaining informed consent from the children's families and, second, the handling and sharing of 'pertinent' and 'incidental' findings by clinicians. It may not be possible to be too prescriptive or objective about these aspects as people's conditions and circumstances vary considerably, but it is nevertheless important that 'guidelines' are developed (preferably at a national level) to ensure that broadly consistent approaches are used throughout the NHS.

With regard to ethical and other frameworks, as well as promoting equity of access (e.g. through centralised commissioning) and issues of data storage, sharing and protection, the following aspects were considered to be important: audit, quality control, accreditation, validation, supervision and mentoring (especially of the new types of staff), clinical governance, professional registration, accredited training and continuing professional development.

Although interviewees recognised that NGS technologies are already quite advanced and are being used quite extensively for research purposes, they did not necessarily consider that they would be adopted particularly quickly (e.g. in the next 3–5 years) for NHS clinical diagnostic work. Views were also mixed on whether or not targeted gene panels would ultimately be superseded by WES, but very few interviewees thought, at least within the foreseeable future, that WGS would be widely adopted by the NHS in clinical settings.

In addition, research should continue to be undertaken to reduce the numbers of false negatives and false positives resulting from the use of NGS technologies.

Cost-effectiveness of next-generation sequencing technologies

Determining the cost-effectiveness of NGS technologies compared with different forms of genetic testing for LDs in children is complicated. First, there is considerable uncertainty around diagnostic yield. This is partly because analysis of the output to produce clinically useful information is still an evolving area of expertise, because of the infancy of the technology. It is also partly because of the heterogeneous nature of the diagnostic pathway of children likely to receive genetic testing and the diversity of the numerous conditions that fall under the definition of LDs. Second, there is a lack of information on the impact of a diagnosis, particularly the impact on a child's ongoing health care, social care and educational support needs. The extent to which care and treatment may be modified as a result of a diagnosis is very variable and is likely to depend on the specific diagnosis. Furthermore, although there is qualitative evidence on the impact of a diagnosis on the child's family, there is a lack of quantitative evidence in this area. Third, the economic implications for education, training and equipment (machines for testing, computer hardware and computer software), of introducing NGS technologies into the NHS are not yet fully understood. Fourth, the costs of NGS technologies appear to be changing on an almost daily basis, with the result that any evaluation will be trying to assess a 'moving target'. In addition, current costs relate to using NGS technologies in a research setting rather than in a clinical setting. This paucity of information means that it is too early in the development process to say whether or not NGS technologies would be cost-effective if used in NHS clinical practice to diagnose LDs in children.

Conclusions

Next-generation sequencing technologies are at an early stage of development and it is too soon to say whether they can offer value for money to the NHS as part of the LD diagnostic process. Stakeholder views differed as to how, and over what time frame, these technologies should be introduced. However, if NGS technologies were introduced, there would be a need for substantial organisational changes. In addition, a number of new systems and safeguards would be required to ensure that the new technologies operate in a safe and equitable manner. Considerable further research is required to establish analytical validity, clinical validity, clinical utility and cost-effectiveness.

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