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Array CGH testing for learning disability- when is it worth it?

This briefing paper presents the results of an economic evaluation comparing the costs and benefits of using array CGH as a first-line test for learning disability within NHS clinical genetics services.

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Learning disability is a significant impairment of the cognitive and adaptive function with onset before the age of 18 years. Around 1.2 to 1.5 million people in England and Wales have a learning disability according to the British Institute of Learning Disabilities and Mencap. This estimate is in agreement with figures of 1 to 3% of the population worldwide. Genetic factors are known to be a significant etiological factor. Technological advances including the use of genome-wide high-resolution microarray comparative genomic hybridisation (array CGH) have led to improved diagnostic capability. Despite compelling evidence of the diagnostic benefits of using array CGH to diagnose learning disability[1] the introduction of array CGH into routine first-line testing of learning disability has been hindered by the perceived high cost and complexity of the test and a lack of consensus on NHS service configuration across laboratories. This is despite the UKGTN approving the first-line use of array CGH for diagnosing learning disability, developmental delay and congenital anomalies for NHS use in 2010[2].

This briefing paper presents the results of an economic evaluation comparing the costs and benefits, as applicable to a NHS clinical genetics service, of using array CGH in a first-line setting with using it as a second-line test following a negative karyotype as the most appropriate comparator.

Methods

This study analysed a retrospective cohort of patients with undiagnosed learning disability and developmental delay consecutively tested by the regional clinical genetics service at Guy's and St Thomas' NHS Foundation Trust as previously reported by Ahn *et al.*[3]. Patients were tested using array CGH either in the first-line strategy or the second-line strategy. A genetic diagnosis was taken as the common outcome measure with the number of diagnoses divided by the total number of patients tested per strategy allowing the percentage diagnoses to be calculated for both testing strategies.

Costs were identified as NHS test prices estimated from the clinical genetics service perspective for the different tests used in the two testing strategies with the assumption that the market prices used are a reasonable approximation of the actual opportunity cost. Patient pathways were created and included clinical appointments and tests undertaken. Costs were limited to the perspective of the genetics service and included both the laboratory and clinical aspects up to the point of the test result. Patient costs were not included. Data on resource use were combined with unit costs for each patient (regardless of outcome) to allow the estimation of the average cost per patient for both of the testing strategies. An incremental cost-effectiveness ratio was calculated as the difference between the costs of the two testing strategies divided by the difference in the number of diagnoses made per testing strategy.
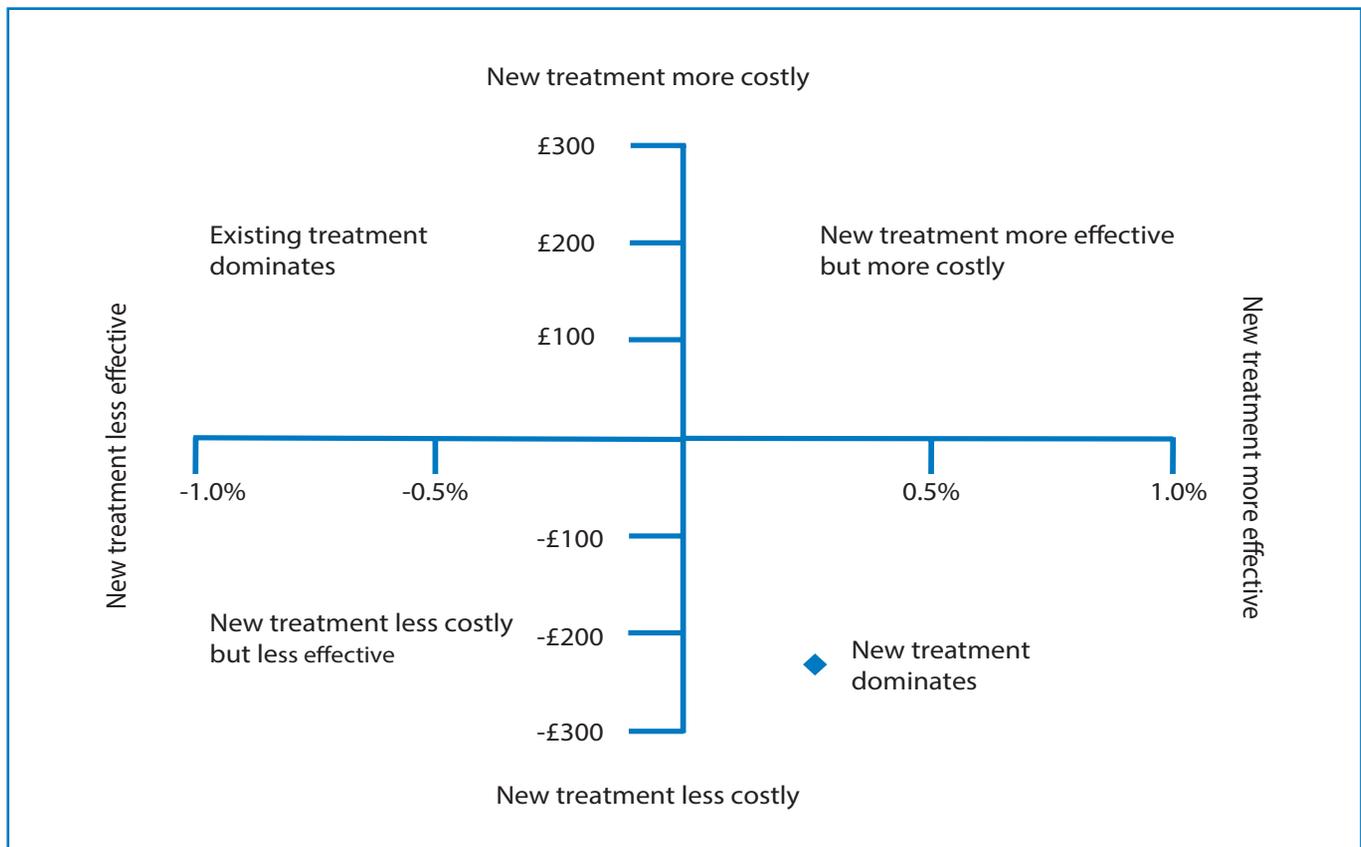
Results

Costs

The mean cost for patients in the first-line test strategy was £291 (ranging from £190 to £1,258). The figure of £190 represents the scenario of testing a patient sample from a clinic other than clinical genetics at Guy's and St Thomas' with the result returned and no clinical follow-up at the genetics service. The mean cost for patients in the second-line test strategy was £533 (ranging from £390 to £1,424). There was a statistically significant difference ($P<0.05$) with a mean incremental cost of -£241.56 (95% confidence interval -£256.93 to -£226.19) which means that using array CGH as a first-line was cost saving.

Benefits

Data were extracted on 848 patients in the array CGH first-line testing strategy and for 742 patients in the second-line testing strategy. In the 1,590 patients tested, 179 genetic diagnoses were made (11.26%) with 97 (11.44%) in the array CGH first-line testing strategy and 82 (11.05%) in the second-line testing strategy. The mean incremental gain in the percentage diagnoses was 0.39% (95% CIs: -2.73% to 3.51%) which meant that using array CGH as a first-line test would produce an additional diagnosis in one patient per 256 patients tested.

Figure 1: Deterministic analysis plotted on the cost-effectiveness plane

New treatment more costly

New treatment less effective

Existing treatment dominates

New treatment more effective but more costly

£300

£200

£100

-1.0%   -0.5%   0.5%   1.0%

-£100

New treatment less costly but less effective

-£200

◆ New treatment dominates

-£300

New treatment more effective

New treatment less costly

Cost-effectiveness

The cost per diagnosis for first-line testing is £2,544.42 versus £4,819.44 for second-line testing (showing the first-line strategy to be £2,275.02 cheaper per diagnosis). The first-line testing strategy costs less and improves diagnostic yield a small amount and is therefore dominant over the second-line testing strategy. However, a negative ICER can be difficult to interpret although this is not necessarily a problem for a deterministic analysis based on a point estimate of differential cost and effect as it is clear in which quadrant the comparison is located (see figure 1). It is possible to move away from a ratio towards a single scale net monetary benefit (NMB) by incorporating an estimated willingness-to-pay per diagnosis threshold[4] into the effect measure and then subtracting the difference in costs between the two strategies from this. A positive NMB would indicate that the evaluated treatment is cost-effective. A statistically significant (P<0.05) positive NMB is produced from our analysis, £272.02 (95% CIs: £32.09 to £511.96), and therefore the first-line testing strategy is cost-effective compared to the second-line testing strategy.

All the sensitivity analyses conducted supported the adoption or dominance of array CGH as a first-line strategy over the second-line strategy

Sensitivity analysis

Sensitivity analyses allow insight into which assumptions or restrictions on the data included are important to the overall conclusion drawn from the analysis. One way analyses were conducted using a pragmatic approach by increasing and decreasing key variables by 25% as this magnitude of change would likely indicate any trends. All the sensitivity analyses conducted supported the adoption or dominance of array CGH as a first-line strategy over the second-line strategy (see table). The difference in diagnostic yield between the two testing strategies was significantly smaller than expected following a review of the published literature (0.39% v 6.2%). This study was conducted in a clinical genetics service that has highly developed clinical and laboratory expertise within this field and as such patients referred to this centre may be more complex and are likely to have undergone other forms of diagnostic testing prior to review at this centre. However, this lower effectiveness did not detrimentally influence the cost-effectiveness of first-line testing in this setting and it may be that other clinical genetics services may see larger savings.

Sensitivity analysis	Incremental cost (£)	Incremental effectiveness (% diagnoses)	Cost-effectiveness
Increase consultant clinical geneticist cost in first-line testing strategy by 25%	-£221.52	0.39%	First-line dominates
Increase laboratory costs for first-line testing strategy by 25%	-£189.25	0.39%	First-line dominates
Increase total cost of first-line testing strategy by 25%	-£168.80	0.39%	First-line dominates
Use literature-based effectiveness estimates for both testing strategies	-£241.56	6.2%	First-line dominates

Conclusion

This briefing note reports a cost-effectiveness analysis comparing the use of array CGH as a first-line test for detecting genomic imbalances that diagnose learning disability versus its use as a second-line test. The first-line testing strategy was shown to dominate the second-line testing strategy and suggests that moving all array CGH testing to first-line in the UK NHS clinical genetics service would be cost-saving. We estimate the regional clinical genetics service at Guy's and St Thomas' NHS Foundation Trust has made an efficiency saving of approximately £2.1 million in clinical and laboratory costs between 2009 and 2013 associated with this specific testing pathway. This was calculated based on 8,794 patients receiving array CGH as a first-line test[5] multiplied by a cost per test saving of £241.56.

The cost savings identified by this analysis only incorporate those directly made by the clinical genetics service. There are also potential costs and savings elsewhere

The cost savings identified by this analysis only incorporate those directly made by the clinical genetics service. There are also potential costs and savings elsewhere within the NHS in addition to the time and cost borne by the parents and/or carers of these patients in attending additional tests and appointments. We have not attempted in this study to capture the impact of an earlier diagnosis for patients and value the potential reduction in time within the diagnostic pathway.

This study shows that using array CGH as a first-line test can reduce the costs to clinical genetics services whilst improving the number of diagnoses achieved. Furthermore, given the advances in DNA sequencing technology, we need to enable the uptake of such advances into NHS clinical pathways in a timelier manner through evidence of clinical effectiveness and cost-effectiveness.

Acknowledgements

References

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