NICE advice

clonoSEQ for minimal residual disease assessment in multiple myeloma, acute lymphoblastic leukaemia and chronic lymphocytic leukaemia

Medtech innovation briefing
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Summary

- The **technology** described in this briefing is clonoSEQ. It is used for assessing minimal residual disease in people with multiple myeloma, acute lymphoblastic leukaemia (ALL) and chronic lymphocytic leukaemia (CLL).
- The **innovative aspects** are that clonoSEQ shows improved standardisation, sensitivity and specificity compared with current techniques. clonoSEQ also uses proprietary bioinformatics and analytics to generate quantitative results from complex datasets.
- The intended **place in therapy** would be during treatment or after remission in people with multiple myeloma, ALL and CLL.

- The **main points from the evidence** summarised in this briefing are from 5 studies: 3 retrospective analyses, 1 prospective cohort study and 1 analytical evaluation of the technology, including 503 people with multiple myeloma, ALL and CLL. They show that the clonoSEQ assay assesses minimal residual disease as an alternative to current clinical practice.
- **Key uncertainties** around the evidence or technology are that none of the studies have been done in an NHS context. The exact cost of the clonoSEQ assay in the UK are not yet available for comparison. There is also a lack of randomised studies in the evidence base. Minimal residual disease assessment is currently standard care in the NHS for people with ALL, but only done for some people with multiple myeloma and CLL.
- **Experts advised** that clonoSEQ is a novel technology and could overcome issues with current methods such as poor sensitivity and analytical difficulties. Two experts highlighted that the value of minimal residual disease assessment to inform clinical decision making is still unclear.
- **Safety issues** identified are potential false positive results or false negative results, which is consistent with all diagnostics.
- The **cost** of clonoSEQ is expected to be in the range of £1,100 to £1,400 per unit (excluding VAT). The **resource impact** would be greater than flow cytometry, which is £300 to £400.

The technology

clonoSEQ (Adaptive Biotechnologies) is a diagnostic medical device. It uses multiplex polymerase chain reaction (PCR) and next generation sequencing (NGS) to differentiate between malignant cells and normal healthy cells. The technology is used to quantify minimal residual disease (MRD) in people with multiple myeloma, acute lymphoblastic leukaemia (ALL) and chronic lymphocytic leukaemia (CLL). MRD is the term given to the small number of leukaemic cells that remain in the blood or bone marrow during treatment, or after treatment when the person is in remission. These cells can eventually cause disease recurrence. MRD assessment is commonly used clinically to evaluate how much the cancer has responded to treatment, categorise the risk of relapse and help decision making. MRD assessment is usually done after initial induction therapy and at additional time points based on the regimen used. The company has stated that people usually have testing for MRD at baseline, and then from 1 to 4 times per year depending on disease

severity. clonoSEQ can identify and track individual cancer cells over time, so each cell's DNA sequence can be assessed in subsequent MRD samples.

Innovations

clonoSEQ uses NGS, which is an alternative to traditional MRD measurement such as flow cytometry. The company claims that NGS has shown enhanced sensitivity and specificity of sequenced-based assays compared with flow cytometry for MRD determination. clonoSEQ uses proprietary bioinformatics and analytics to generate clinically relevant and quantitative results from complex datasets. Also, laboratories using standard techniques may use different preparation procedures, reagents and reporting methods, which is a significant limitation in terms of standardisation. NGS is intended to address these issues.

Current care pathway

Clinical feedback suggests that MRD testing is standard practice across treatment centres in England for people with ALL. It is only done for certain people with multiple myeloma and CLL. MRD status is a major predictive factor of relapse for people in remission, so MRD assessment is usually done after starting induction therapy when complete remission is first seen. Current methods of MRD assessment include flow cytometry and PCR. Flow cytometry is a technique when antibodies are used to bind to different cell markers on cells. These antibodies are tagged with a fluorescent molecule to be detected and allow specific proteins to be identified on the cell. PCR also uses fluorescent markers to bind to newly synthesised DNA strands from a specific gene of interest.

The following publications have been identified as relevant to this care pathway:

- NICE's guideline on myeloma: diagnosis and management
- NICE's guideline on haematological cancers: improving outcomes
- NICE's quality standard on haematological cancers
- NICE Pathway on myeloma
- NICE Pathway on blood and bone marrow cancers
- NICE's technology appraisal guidance on blinatumomab for treating acute lymphoblastic leukaemia in remission with minimal residual disease activity.

Population, setting and intended user

clonoSEQ is intended for people with multiple myeloma, ALL and CLL during treatment or after remission. For multiple myeloma, MRD testing is not usually done until a person is in complete remission. The technology is likely to be used in specialist centres by haematologists or oncologists.

Costs

Technology costs

The cost of the clonoSEQ assay has not yet been decided in the UK. The company has advised that the list price of the assay in the UK will be in the range of £1,100 to £1,400 per unit.

Costs of standard care

The cost of MRD assessment using flow cytometry is £300 to £400 per unit. This estimate is based on expert input received by the company from 3 NHS myeloma oncologists. PCR is not commonly used in the UK.

Resource consequences

The technology is not currently used in the NHS, but the company estimates that about 50,000 to 75,000 people a year would be eligible for MRD assessment using clonoSEQ.

It is unclear whether any changes in facilities or infrastructure would be needed with adoption of the technology.

Regulatory information

clonoSEQ is a CE-marked class III medical device.

The following manufacturer field safety notices or medical device alerts for this technology have been identified and are consistent with all diagnostics:

- false positive results
- false negative results.

Equality considerations

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

No equality issues were identified during the development of this briefing.

Clinical and technical evidence

A literature search was carried out for this briefing in accordance with the interim process and methods statement. This briefing includes the most relevant or best available published evidence relating to the clinical effectiveness of the technology. Further information about how the evidence for this briefing was selected is available on request by contacting mibs@nice.org.uk.

Published evidence

Five studies are summarised in this briefing. There are several other studies that have not been summarised in this briefing. We have focused on published comparative and validation studies with the best methodological quality and largest study populations.

Three retrospective analyses of 269 people (Perrot et al. 2018), 133 people (Martinez-Lopez et al. 2014) and 125 people (Takamatsu et al. 2017) with multiple myeloma are included. One prospective cohort study of 110 children (Faham et al. 2012) with newly diagnosed ALL in the US is summarised. An analytical evaluation of 66 people (Ching et al. 2020) with ALL, CLL and multiple myeloma is also included.

The clinical evidence and its strengths and limitations is summarised in the overall assessment of the evidence.

Overall assessment of the evidence

The evidence base for the clonoSEQ assay consists of a few large studies with many smaller studies. Several analytical studies have been done to determine the specificity and sensitivity of the technology when used as a diagnostic tool. The primary outcomes in the studies mainly assess survival and time to progression based on MRD status. Many comparative studies have been done between NGS and the 2 current methods for MRD assessment, multiparametric flow cytometry (MFC) and allele-specific oligonucleotide-polymerase chain reaction (ASO-PCR). None of the studies are in a UK or NHS context, but some have been done in Europe and the US. Most of the studies are retrospective analyses or cohort studies, no randomised controlled trials were found.

Studies on sequencing assays have been done across all 3 of the patient groups specified by the company: multiple myeloma, ALL and CLL. In addition, both adults and children are included in the evidence base. Overall, the evidence suggests that NGS is a useful method for MRD assessment, with higher levels of sensitivity than methods it has been compared with. The technology has been shown to be accurate when more than 1 in 1,000,000 cells are malignant. The evidence base consists of independent studies and studies funded by the company.

Perrot et al. (2018)

Study size, design and location

Retrospective analysis of bone marrow samples from 269 people with multiple myeloma to detect MRD using NGS and MFC. The study was done in France, Belgium and Switzerland.

Intervention and comparator

NGS (clonoSEQ) compared with MFC and ASO-PCR.

Key outcomes

MRD assessment was completed in 224 people at the start of maintenance therapy and 183 people after completion. Before maintenance therapy, MRD status was found to predict progression-free survival (PFS; hazard ratio 0.22, $p<0.001$) and overall survival (OS; hazard ratio 0.24, $p=0.001$). After maintenance therapy MRD was also predictive of PFS

(p<0.001) and OS (p=0.008). People who tested negative for MRD had a higher probability of prolonged PFS than people with detectable residual disease, regardless of treatment group or risk profile at diagnosis. People with the deepest level of MRD-negativity ($<10^{-6}$) had longer PFS than people with higher levels of disease burden (both before and after maintenance; p<0.001). People who still tested negative for MRD after maintenance had better PFS and OS than people who had MRD before and after maintenance or tested positive for MRD after maintenance. There were 429 samples (75%) that were tested with clonoSEQ that had the same result as testing with MFC. There were 143 results that were different between the 2 methods. Of these, 133 samples tested positive for MRD with clonoSEQ and negative with MFC, while 10 samples tested negative for MRD with clonoSEQ and positive with MFC.

Strengths and limitations

A significant limitation of this study was that NGS was only compared with MFC by assessing whether results were the same using both tests. No analysis was done to follow the OS or PFS of people who had results that differed between clonoSEQ and MFC. This would have shown whether NGS or MFC MRD assessment is a more reliable indicator of patient outcomes. The follow-up period used was median 50 months after initial maintenance therapy, which is relatively long. The study also used a large sample size, with 562 samples from 269 people.

Martinez-Lopez et al. (2014)

Study size, design and location

Retrospective analysis of bone marrow samples from 133 people with multiple myeloma to detect MRD using NGS, MFC and ASO-PCR in Spain.

Intervention and comparators

NGS (clonoSEQ), compared with MFC and ASO-PCR.

Key outcomes

People who were found to not have MRD with clonoSEQ had a significantly longer time to tumour progression (TTP) than those who had MRD (median 80 months compared with 31 months, p<0.0001) and better OS (median not reached compared with 81 months,

p=0.02). When classifying different levels of MRD in people the TTP medians were:

- MRD above 10^{-3}, 27 months
- MRD 10^{-3} to 10^{-5}, 48 months
- MRD below 10^{-5}, 80 months.

Similarly, MRD below 10^{-5} was associated with significantly longer OS compared with MRD above 10^{-3} (median not reached compared with 55 months, p=0.002).

MRD information from MFC and ASO-PCR analysis was available in 99 and 41 people, respectively. Results were concordant in 83% of samples between NGS and MFC, and in 85% of samples between NGS and ASO-PCR. To assess the clinical significance of difference between methods, a comparison was made for the 99 people who had MRD results using both sequencing and MFC. There were 82 people who had the same results (60 double-positives and 22 double-negatives), whereas 12 tested negative for MRD with MFC and positive with clonoSEQ. For the comparison with clonoSEQ negative cases (median TTP not reached), MFC negative or clonoSEQ positive cases had a TTP of median 50 months (p=0.05). Of the 5 remaining people who tested positive for MRD with MFC and negative with clonoSEQ, only 1 person had disease progression during the study follow-up period.

Strengths and limitations

A significant limitation of this study was that time to progression was only compared between NGS and MFC, despite 41 people having both NGS and ASO-PCR results available. Also, the length of the follow-up period was not stated. A strength of this study was the focus on TTP as an outcome, which is an important consideration for people with multiple myeloma. Classifying results by amount of MRD is another significant strength, because this provides further evidence of the high sensitivity of NGS when comparing outcomes between the 3 groups.

Faham et al. (2012)

Study size, design and location

Comparative study of 110 children with newly diagnosed ALL to detect MRD using NGS, flow cytometry and ASO-PCR in the US.

Intervention and comparators

NGS compared with MFC and ASO-PCR.

Key outcomes

Technical performance of the assay was tested using diagnostic samples from 12 of the 110 people with ALL. Serial dilutions of leukaemic cells ranging from less than 1 in 1,000,000 cells to less than 1 in 1,000 cells were prepared and analysed. The assay was highly quantitative for frequencies above 10^{-5}, random error increased at clonotype frequencies below 10^{-5}. The assay showed high r^2 values (median 0.9991, range 0.977 to 0.996) between each of the expected and measured clonotype frequencies. The cell dilution experiments showed that the assay was quantitative with sensitivity levels at or below 1 malignant cell in 1,000,000.

MRD was assessed in follow-up samples during therapy from 106 children. Concordance was tested between MRD results obtained by the assay and flow cytometry, which was used in 105 of the 106 children. The 2 methods gave concordant positive or negative MRD results in 95 out of 105 samples (90%). In 10 samples (10%), MRD was positive with clonoSEQ but undetectable by flow cytometry. MRD levels ranged between 0.00004% and 0.011% by sequencing in 9 of the 10 samples, 7 of these were also positive with ASO-PCR. Results between the assay and ASO-PCR were concordant in 102 of 106 follow-up samples (96%). In 3 samples, MRD was positive with clonoSEQ but undetectable by ASO-PCR. The remaining sample was detected as 0.002% by ASO-PCR but undetectable by sequencing.

Strengths and limitations

A strength of this study is that it tested samples from children rather than adults, across the evidence base there are no comparative studies that use a large population of children. The comparison between the assay and 2 different methods was done without knowledge of the results beforehand, this aspect of blinding reduces the chance of bias. The dilution study used to test the sensitivity of the assay is also useful in this study population.

Takamatsu et al. (2017)

Study size, design and location

Retrospective analysis of 125 people with multiple myeloma to detect MRD using NGS and ASO-PCR with a median follow up of 3.5 years in Japan.

Intervention and comparator

NGS (clonoSEQ) compared with ASO-PCR.

Key outcomes

There were 68 autograft and 25 bone marrow samples assessed with both MRD assessment methods. There were 35 samples that tested positive for MRD with NGS and tested negative for MRD with ASO-PCR. This was consistent with the higher sensitivity of the NGS method (10^{-6} compared with 10^{-4} to 10^{-5}). A high correlation was seen between NGS and ASO-PCR results at MRD levels of 10^{-5} or higher (r=0.618, p=0.005).

The researchers investigated whether people whose autografts tested positive for MRD with NGS and negative with PCR have different prognosis from those whose autografts tested negative with NGS. PFS was compared in 7 NGS-MRD negative autograft cases (group 1) with 11 NGS-MRD positive and ASO-PCR MRD negative cases (group 2). People in group 1 showed significantly better PFS than people in group 2 (p=0.018). There was no difference in OS between the 2 groups, which was 100% for both. PFS was also compared in the 7 NGS-MRD positive and ASO-PCR MRD negative cases (group 2) with 12 NGS-MRD negative bone marrow cases (group 3). People in group 3 showed significantly better PFS than people in group 4 (p=0.001), but there was no difference in OS (both 100%).

Strengths and limitations

The major limitations of this study are the relatively small sample size and retrospective nature of the analysis, rather than prospective. Also, some of the authors are employees of the company. A strength of the study is the comparison of MRD assessment between NGS and ASO-PCR in 2 different types of tissue, autograft and bone marrow. MRD status is most often used as a predictor of OS or PFS, the 2 primary outcomes that were investigated in this comparison.

Ching et al. (2020)

Study size, design and location

Analytical evaluation of the clonoSEQ assay for establishing MRD in 66 people with ALL, CLL or multiple myeloma in the US.

Intervention and comparator

NGS (clonoSEQ) compared with MFC.

Key outcomes

The analysis aimed to determine the sensitivity and specificity of clonoSEQ by assessing the limit of detection (LoD), limit of quantitation (LoQ) and the limit of blank (LoB). LoD was defined as the malignant cell count at which the assay would detect MRD in 95% of samples. LoQ was defined as the lowest clonoSEQ sample MRD frequency that could be determined within 70% relative total error. LoB was the probability that a non-malignant clone would not be excluded, which could lead to false detection or an inflated estimate of MRD. Results were based on combined data from ALL, CLL and multiple myeloma samples at 2 DNA input levels (500 nanograms and 20 micrograms).

The LoD of the clonoSEQ assay was estimated to be 1.903 malignant cells at an input level of 20 micrograms of DNA and the LoQ was 2.39 malignant cells. Follow-up studies confirmed the LoD and LoQ across total DNA inputs ranging from 200 nanograms to 40 micrograms. The LoB of the assay was 0 at both 500 nanograms and 20 micrograms of healthy donor DNA. This confirmed that less than 5% of MRD measurements in healthy samples produce non-zero values. Comparison between the clonoSEQ assay and MFC measurements showed similar quantitative accuracy across the tested range, particularly at MRD frequencies above 10^{-4} (r^2=0.98). Relative bias between disease burden increased at lower cell inputs, a test range that spans clonoSEQ's LoQ (2.39 cells).

Strengths and limitations

A significant strength of this study is that sensitivity and specificity of the clonoSEQ assay was assessed in all 3 disease groups: ALL, CLL and multiple myeloma. A comparative analysis with MFC showed that clonoSEQ identified cells at lower input levels. The authors stated that a subgroup of people with B-cell precursor ALL need other methods of MRD

monitoring. A limitation of the study is that it was wholly funded by the company.

Sustainability

No sustainability benefits have been identified by the company.

Recent and ongoing studies

- The clonoSEQ Watch Registry: a prospective, multi-centre, observational study of adults with a diagnosis of ALL, multiple myeloma, CLL or non-Hodgkin lymphoma. ClinicalTrials.gov identifier: NCT04545333. Status: ongoing, recruiting. Indications: multiple myeloma, ALL, CLL, non-Hodgkin lymphoma. Device: clonoSEQ. Estimated completion date: April 2024. Location: the US.
- DNA sequencing-based monitoring of MRD to predict clinical relapse in aggressive B-cell non-Hodgkin lymphomas. ClinicalTrials.gov identifier: NCT02633111. Status: active, not recruiting. Indication: B-cell non-Hodgkin lymphoma. Device: clonoSEQ. Estimated completion date: October 2023. Location: the US.
- Study to assess for MRD in multiple myeloma to determine if MRD-negativity allows people to stop post-transplant maintenance therapy after having at least 1 year of maintenance therapy. ClinicalTrials.gov identifier: NCT04108624. Status: active, recruiting. Indication: multiple myeloma. Device: clonoSEQ. Estimated completion date: December 2024. Location: the US.

Expert comments

Comments on this technology were invited from clinical experts working in the field and relevant patient organisations. The comments received are individual opinions and do not represent NICE's view.

One out of 5 experts were familiar with or had used this technology before.

Level of innovation

All of the experts agreed that the technology is novel compared with standard care and is expected to be used as an alternative to established methods such as flow cytometry. One

of the experts explained that clonoSEQ is based on a combination of highly optimised multiplex polymerase chain reaction and next generation sequencing (NGS) with internal controls. The elements themselves are not novel, but the combination of them and optimisation for specific cases is what makes the technology novel. Three of the experts commented on issues with current methods such as poor sensitivity and analytical difficulties, which could be overcome by NGS.

Potential patient impact

Four of the experts said that the technology is more sensitive than standard care. This offers the possibility to detect lower levels of minimal residual disease (MRD), giving a more accurate prognosis to allow personalised decision making for precise treatment. One of the experts explained that clinical trials are ongoing to establish whether MRD is useful to make treatment decisions for multiple myeloma and chronic lymphoblastic leukaemia. Another expert said that MRD is only relevant for people who are already in complete remission. One expert also said that adults currently have a much higher failure rate of marker identification compared with children. NGS may show enhanced performance of marker identification in this group.

Potential system impact

One of the experts explained that the technology can provide more equal access to MRD assessment, which is only available through clinical trials for most people. Two experts stated that the technology and MRD as a whole need further verification before being used to inform clinical decision making. They also said that the technology is likely to cost significantly more than standard care, both because of the cost of the test and training. The other 3 experts acknowledged that the assay may cost more upfront but said that the costs of the assay will offset current system costs and significant cost savings will be seen downstream for all 3 indications.

General comments

Three of the experts commented that clinical facilities may need to be upgraded if clonoSEQ was adopted in the NHS. Clinicians will also need additional training to use clonoSEQ, which is provided by Adaptive Biotechnologies. Three experts also outlined the potential harms of false positives and false negatives, which could lead to over- or under-treatment. These risks are present with other diagnostic technologies too. If clonoSEQ is

adopted, 4 of the 5 experts expect the technology to be used in fewer than 10 specialist centres across the UK.

Expert commentators

The following clinicians contributed to this briefing:

- Professor Anna Schuh, director of molecular diagnostics and consultant haematologist, University of Oxford and Oxford University Hospitals NHS Trust. Received educational grants and honoraria for advisory boards from the company.
- Professor Guy Pratt, honorary professor of haematology and consultant haematologist, University Hospitals Birmingham NHS Foundation Trust. Did not declare any interests.
- Dr Karthik Ramasamy, associate professor of haematology and consultant haematologist, University of Oxford and Oxford University Hospitals NHS Trust. Received honoraria from the company for attending advisory boards.
- Dr Bela Wrench, group leader in leukaemia biology and honorary consultant in haemato-oncology, Barts Cancer Institute. Did not declare any interests.
- Dr John Riches, consultant haemato-oncologist, Barts Cancer Institute. Did not declare any interests.

Development of this briefing

This briefing was developed by NICE. The interim process and methods statement sets out the process NICE uses to select topics, and how the briefings are developed, quality-assured and approved for publication.

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