Healthcare Improvement Scotland | SHTG Advice on health technologies

Innovative Medical Technology Overview

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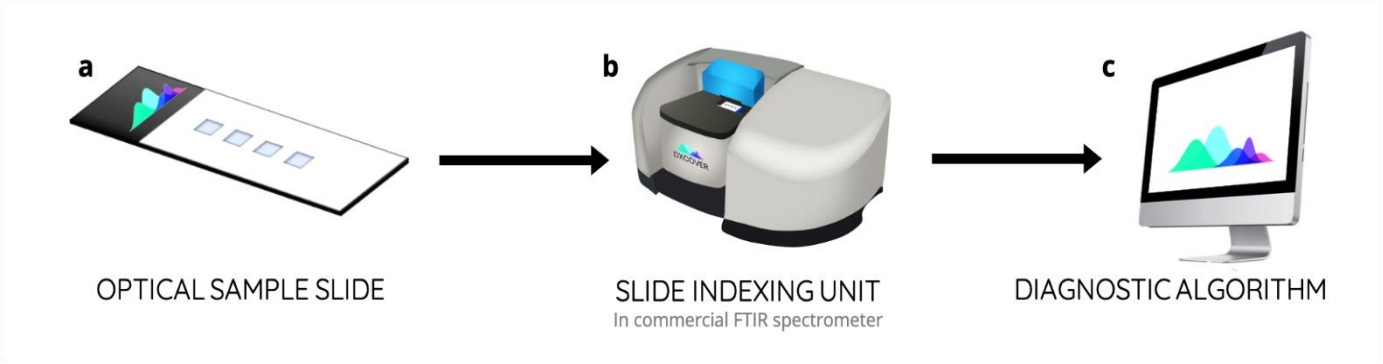
Dxcover™ brain cancer liquid biopsy test for early brain cancer detection in primary care.



Executive summary

The Scottish Health Technologies Group (SHTG) was asked by the developers of Dxcover™ to assess the evidence for a liquid biopsy test which aims to improve the assessment of brain tumour risk by identifying those most likely to benefit from urgent imaging.

Triage of patients with signs and symptoms that may indicate a brain tumour in primary care is challenging due to the common and non-specific nature of the presenting symptoms. Patients frequently visit with their general practitioner (GP) several times before a diagnosis is reached.

In a published diagnostic accuracy cohort study (n=385) undertaken in secondary care that included 64 patients with known brain tumours, the Dxcover™ test was able to distinguish between patients with and without brain cancer. Negative predictive value (the proportion of those testing negative who did not have a tumour) was 95% and positive predictive value (the proportion of those testing positive who had a tumour) was 45%.

An exploratory cost-effectiveness model based on early pre-trial data suggested the test was likely to be cost-effective if the prevalence of brain cancer in the primary care population being considered for referral was 1% or higher and a test cost of £100 was assumed. Clinical opinion suggests uncertainty around the prevalence of brain cancer in the target population.

Further work is required to:

- confirm the accuracy of the test in a primary care population
- assess the effect of the test on patient pathways
- examine impact on patient outcomes and
- define the cost effectiveness.

Technology and innovative aspect

The Dxcover™ brain cancer liquid biopsy test uses machine learning to identify and compare patterns in the biochemical profile of serum from patients with and without brain cancer. This is measured by the response of biological materials in the sample to different wavelengths of light (attenuated total reflection (ATR)-Fourier transform infrared (FTIR) spectroscopy).[1] The test uses diagnostic algorithms to analyse spectra from samples provided by patients suspected of having brain cancer to predict which patients are likely to have the disease.

There is no biomarker test for brain tumours. The innovative aspect of this test is that, rather than focusing on a single biomarker for disease, the test algorithm utilises the full biological profile of the serum sample. No specialist sample preparation is required and results are available within minutes.

The technology is being developed under an ISO13485 design control process (certification audit October 2021) and is in late stage technical development. UK-CA marking under in vitro diagnostic directive (IVDD) will be applied for.

Target patient group

The patient group is people who present to primary care with non-specific symptoms, such as headache and or dizziness, which may be related to brain cancer and where there is

uncertainty as to the need for a GP to refer for medical imaging. The test is intended to improve triage and enhance the prioritisation of patients most likely to have brain cancer.

Current practice: comparators and use of technology in pathway of care

Early diagnosis of brain cancer is challenging due to the number of patients presenting to primary care with common and non-specific symptoms. Many patients with brain cancer visit their GP several times before a diagnosis.[2] In one Scottish study of 2,938 head scans, only 1.8% of patients referred from primary care for direct-access computed tomography (CT) were found to have intracranial tumours. The symptom-based referral guidelines used in the study had a positive predictive value (PPV) of 3%.[3]

The influence of late diagnosis on outcomes is unclear. The impact of time from first presenting symptom to specialist review and/or imaging on patient outcomes is likely to vary according to tumour biology.[4, 5] Delays to diagnosis and the perceived influence of these on outcomes are distressing for patients and their families and can have a significant detrimental effect on mental health and quality of life.

In Scotland, there is variation in current practice in how patients with brain cancer are identified. The Scottish Referral Guidelines for Suspected Cancer recommend, as good practice, that all NHS Boards have pathways for investigation of headaches, which should include primary care direct access to imaging.[6] Diagnosis may also follow referral for specialist neurology or ophthalmology assessment or to the emergency department. Patients may also be diagnosed via attendance at or admission through the emergency department with clinical deterioration or urgent symptoms such as seizures.

Product performance: published data

A single-centre diagnostic accuracy cohort study undertook consecutive recruitment of two patient groups in secondary care (total n=385, distribution not provided – calculated from prevalence):[7]

- Symptomatic patients (age ≥16 years, n=321) who were referred from primary care to a direct-access CT service to exclude significant intracranial pathology. Patients were not urgent (same-day) referrals.
- Secondary care patients (age ≥16 years, n=64) with a recent diagnosis of primary or recurrent brain tumour.

The study population in this clinical feasibility study did not match the intended target population of patients in primary care most likely to benefit from earlier referral where the test may inform referral decisions.

Serum samples were analysed using Dxcover™ spectroscopic liquid biopsy as the index test. Samples for analysis were anonymised and the test was conducted blind to the reference standard. The reference standard was CT imaging to confirm or refute evidence of central nervous system tumours, followed by diagnosis by biopsy if clinically indicated.

For the total cohort, the prevalence of brain tumours was 17%. The sensitivity of Dxcover™ was 81% (95% confidence interval (CI) 71% to 90%) giving a PPV of 45%. The specificity was 80% (95%CI 75% to 84%) leading to a negative predictive value of 95%.

There were three cases in the group of patients referred from primary care (0.9%). The cohort was enriched with patients with known brain cancer (most commonly glioblastoma) to provide positive events for assessment of test performance and provide a training dataset to further develop the diagnostic algorithm.

Unpublished and ongoing studies

An unpublished diagnostic accuracy cohort study recruited three patient groups (total n=603, distribution not provided):[8]

- Symptomatic patients (age ≥16 years) who were referred from primary care to a direct-access CT service to exclude significant intracranial pathology. Patients were not urgent (same-day) referrals.
- Patients (age ≥16 years) presenting to the emergency department with a new onset neurological symptom, with no history of trauma, where the assessing clinician judged brain imaging was necessary and that the differential diagnosis included a brain tumour.
- Patients with a new brain tumour diagnosis, scheduled for surgery, were also invited to participate prior to surgery.

Samples were anonymised for processing and analysis. Data interpretation was blinded to brain imaging and histological diagnosis; imaging outcomes were recorded from the formal radiological report and histological tumour diagnosis was available for patients who underwent surgery.

The diagnostic algorithm (which was designated as Model 603) was retrospectively tuned to optimise sensitivity or specificity. The corresponding results are summarised in *Table 1.*

Table 1: summarised results of Dxcover™ Model 603

	Sensitivity	Specificity
Sensitivity tuned	96%	45%
Specificity tuned	47%	90%

These data were applied in illustrative clinical scenarios to a primary care population of 10,000 patients being considered for referral for imaging, with a 1% prevalence of brain tumour (see *Table 2*). In the scenarios, it was assumed, based on clinical expert opinion, that 50% of

patients who receive a negative test result will still be referred for imaging based on symptom profile and other non-tumour diagnoses being considered by the clinician. Emergency referral was defined as referral with a median time to diagnosis of 8 days. The results and potential patient impact for each tuning option are summarised in *Table 2.*

The table shows that among 10,000 patients being tested, 100 have brain tumours. When tuned for maximum sensitivity, 96 of these patients will receive a positive test result and have an emergency referral to imaging for confirmation of the diagnosis. Their diagnosis will be quicker than standard care where they would have waited an average of around four weeks for imaging. Two patients will receive a negative result and a standard referral to imaging. The timing of their diagnosis will be identical to what would happen without a liquid biopsy test. Another two patients will receive a negative result and not be referred to imaging. They will only be referred if they present again with persistent or additional symptoms.

Among the 9,900 patients that do not have a brain tumour, 4,455 patients will receive a negative result. Among this group, 2,227 patients will not be referred to an imaging test that they would have needed, while the other 2,228 patients will receive a standard referral to imaging. The remaining 5,445 patients without tumours who had a positive result will receive an emergency referral for imaging.

Table 2: Clinical scenarios of Dxcover™ Model 603 applied to a primary care referral population

		Sensitivity tuned	Specificity tuned	Patient impact
Patients with brain cancer (n=100)	Test positive emergency referral	96	47	Diagnosed earlier than standard care
	Test negative non-urgent referral based on clinical symptoms	2	27	Diagnosed at same time as standard care
	Test negative no further testing	2	26	Diagnosed later than standard care
Patients without brain cancer (n=9,900)	Test positive emergency referral	5,445	990	Experience more urgent imaging than standard care
	Test negative non-urgent referral based on clinical symptoms	2,228	4,455	Experience imaging at the same time as standard care

	Test negative no further testing	2,227	4,455	Avoid unnecessary imaging

Safety

The main safety issues are around the potential impact of false positive and false negative results on psychological distress. For patients receiving a false negative result this may lead to delays in referral for imaging and a later diagnosis than if the test were not used. Patients receiving a false positive result may experience unnecessary imaging.

No safety issues around use of the technology by healthcare professionals were identified by the developers.

Economic and cost considerations

An exploratory pre-trial, model-based economic analysis[9] used Dxcover™ sensitivity (92.8%) and specificity (91.5%) data derived from a proof of concept retrospective case-control study using tissue-bank samples from patients with and without brain cancer.[10]

A decision tree was used to model the pathway for patients presenting in primary care with symptoms warranting a referral for magnetic resonance imaging (MRI) or CT for suspected brain tumour. See Figure *1.*

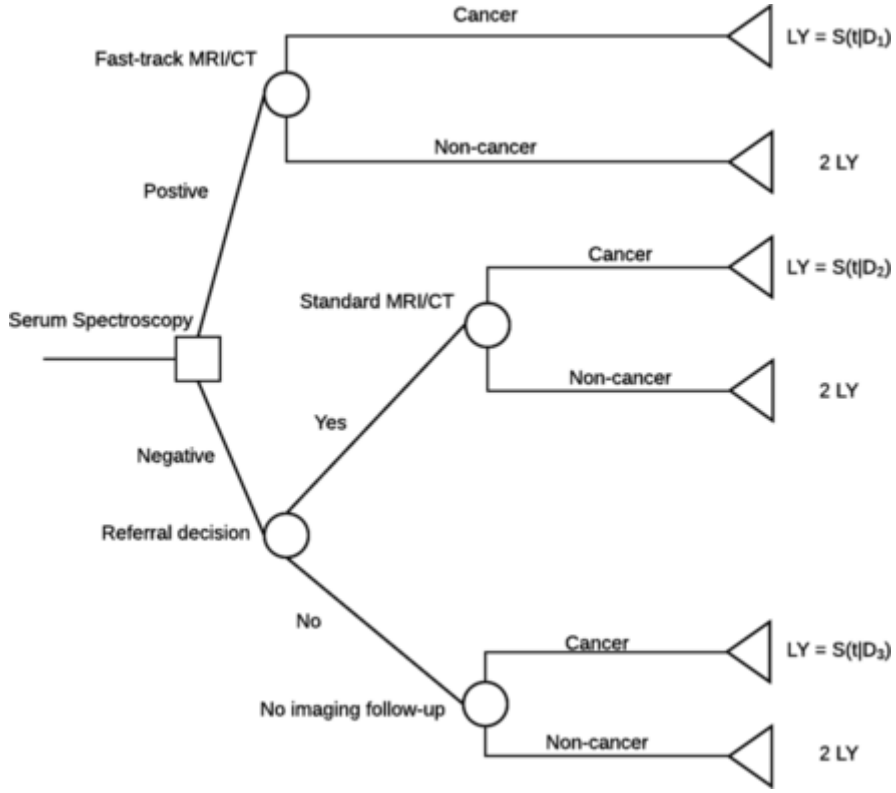


Figure 1: A decision tree model describing the integration of a serum spectroscopy test in the current diagnostic pathway, and the effect on MRI/CT imaging for suspected brain tumour. D1, 1 week; D2, 4 weeks; D3, 8 weeks; LY, life year; S(t|D), survival time in days conditional on 'delay'.

A 2-year time horizon was selected due to the short duration of survival of patients with the most common malignant primary brain tumour (glioblastoma). Key assumptions included:

- the expected time to diagnosis would match the current median time to diagnosis in emergency care
- all patients referred to secondary care would continue to imaging
- 50% of patients testing negative with Dxcover™ would continue to imaging based on clinical judgement, and
- potential benefits of earlier diagnosis are consistent with those extrapolated from observational data in patients with high-grade glioma.

The total volume of tests in the primary care triage setting was estimated at 75,000 per year in the United Kingdom, whilst for secondary care triage the number was estimated at 53,000.

As a triage tool in both primary care (prevalence 0.5%) and in secondary care (prevalence 3%) to reduce diagnostic delays, the incremental cost-effectiveness ratios (ICERs) were well below the standard threshold values of £20k to £30k per quality adjusted life year (QALY) provided that the test cost less than £100.

This model was updated to incorporate the results of a prospective test validation study where the test sensitivity was 81% and the specificity 80%. Primary care prevalence was set at 1% and secondary care at 3%.[11] Assuming a test cost of £100, the ICER was £13,279 for use in primary care and £22,197 for use in secondary care. Both disease prevalence and hazard ratio for delay

to diagnosis were highly influential in one-way sensitivity analyses. For example, at a test cost of £100, if prevalence estimate was 0.5% instead of 1% for primary care, then the ICER would be >£20,000 and the technology may not be considered cost-effective.

The cost-effectiveness analyses are limited by the lack of direct evidence of the effect of alternative diagnostic pathways on patient survival and quality of life.

Recommendations for further research

A study in the target primary care population is required to assess:

- the accuracy of the test in the target setting
- its acceptability to patients, GPs and secondary care specialists
- the extent to which it influences referral decisions
- impact on patient outcomes, and
- its cost effectiveness in routine primary care and its impact on secondary care pathways.

Conclusions

Preliminary evidence suggests that further work is needed to establish whether or not Dxcover™ has the potential to be a cost-effective tool to improve triage of patients in primary care and facilitate earlier referral for diagnostic imaging. The current evidence base includes a number of assumptions around brain cancer prevalence and referral behaviours in response to test results. Firm conclusions cannot be drawn without further evaluation within the general practice setting.

References

1. Butler HJ, Brennan PM, Cameron JM, Finlayson D, Hegarty MG, Jenkinson MD*, et al.* Development of high-throughput ATR-FTIR technology for rapid triage of brain cancer. Nat Commun. 2019;10(1):4501.
2. Ozawa M, Brennan PM, Zienius K, Kurian KM, Hollingworth W, Weller D*, et al.* The usefulness of symptoms alone or combined for general practitioners in considering the diagnosis of a brain tumour: a case-control study using the clinical practice research database (CPRD) (2000-2014). BMJ Open. 2019;9(8).
3. Zienius K, Chak-Lam I, Park J, Ozawa M, Hamilton W, Weller D*, et al.* Direct access CT for suspicion of brain tumour: an analysis of referral pathways in a population-based patient group. BMC Fam Pract. 2019;20(1):118.
4. Aggarwal A, Herz N, Campbell P, Arkush L, Short S, Rees J. Diagnostic delay and survival in high-grade gliomas–evidence of the 'waiting time paradox'? Br J Neurosurg. 2015;29(4):520-3.
5. Kosmin M, Solda' F, Wilson E, Kitchen N, Rees J, Fersht N. The impact of route of diagnosis on survival in patients with glioblastoma. Br J Neurosurg. 2018;32(6):628-30.

6. Scottish Government. Scottish referral guidelines for suspected cancer. 2019 [cited 25 June 2021]; Available from: http://www.cancerreferral.scot.nhs.uk/brain-and-central-nervous-system-cancers/.
7. Brennan PM, Butler HJ, Christie L, Hegarty MG, Jenkinson MD, Keerie C*, et al.* Early diagnosis of brain tumours using a novel spectroscopic liquid biopsy. Brain Commun. 2021;3(2):fcab056.
8. Baker M J et al. Brain-ED2 Final Report, Dxcover Ltd
9. Gray E, Butler HJ, Board R, Brennan PM, Chalmers AJ, Dawson T*, et al.* Health economic evaluation of a serum-based blood test for brain tumour diagnosis: exploration of two clinical scenarios. BMJ Open. 2018;8(5):e017593.
10. Smith BR, Ashton KM, Brodbelt A, Dawson T, Jenkinson MD, Hunt NT*, et al.* Combining random forest and 2D correlation analysis to identify serum spectral signatures for neuro-oncology. Analyst. 2016;141(12):3668-78.
11. Gray E, Cameron JM, Butler HJ, Jenkinson MD, Hegarty MG, Palmer DS*, et al.* Early economic evaluation to guide the development of a spectroscopic liquid biopsy for the detection of brain cancer. Int J Technol Assess Health Care. 2021;37:e41.

Acknowledgment of professional commentators, fact checking and patient organisational input

Professional commentary was provided by:

- A consultant neurosurgeon, NHSScotland, and
- Three general practitioners, NHSScotland.

Fact checking was conducted by the Chief Technical Officer & Co-Founder of Dxcover Ltd

Input was provided by the Brain Tumour Charity.

Declarations of interests were obtained from professional commentators and the Brain Tumour Charity.

What is an IMTO?

An IMTO provides a high-level summary of the evidence surrounding health and care innovation in Scotland. IMTOs may include:

- a review of local evaluation(s) undertaken within NHSScotland
- an appraisal of the evidence, based on the health technology assessment framework
- bespoke analysis and advice towards the development of evidence.

The purpose of an IMTO is to raise awareness of promising innovations and to assist local decision making by health and care colleagues. Further information about the IMTO process can be found on the SHTG webpage.