Technoleg Iechyd Cymru
Health Technology Wales

Topic Exploration Report

Topic explorations are designed to provide a high-level briefing on new topics submitted for consideration by Health Technology Wales. The main objectives of this report are to:

1. Determine the quantity and quality of evidence available for a technology of interest.
2. Identify any gaps in the evidence/ongoing evidence collection.
3. Inform decisions on topics that warrant fuller assessment by Health Technology Wales.

Topic:	Rapid fully-automated PCR testing (Idylla) to screen for BRAF mutational status in people with melanoma
Topic exploration report number:	TER191.2

Introduction and aims

The Idylla platform is a PCR machine that allows for rapid (2 to 3 hour), fully-automated PCR testing for various genetic abnormalities, which can then inform appropriate oncological treatment. At the time of this report there are seven PCR assays available for the Idylla system, and a further one in development.

For this report, Health Technology Wales researchers searched for evidence on rapid, fully-automated PCR testing (such as Idylla) to determine BRAF mutational status in melanoma. BRAF mutations are found in about 50% of melanoma cases, and knowledge of this mutational status can inform appropriate treatment. Note that Idylla provides two assays that include BRAF mutational status: the BRAF assay and the NRAS/BRAF assay; this topic exploration focusses on the BRAF assay.

This report is one of two topic explorations on the Idylla system, exploring two different tests (EGFR test and BRAF test).

Summary of evidence

Guidelines

We identified guidelines that recommend treatment regimens based on BRAF mutational status from the Health Technology Assessment Group in Ireland, SIGN and the National Institute for Health and Care Excellence (NICE). SIGN guidelines recommend that BRAF status be requested for all patients with advanced melanoma.

Secondary evidence

We did not identify any secondary evidence on rapid, fully-automated PCR testing for BRAF mutational status in melanoma.

Primary evidence

We identified seven primary studies evaluating the Idylla system for BRAF testing in melanoma. This included five retrospective and one prospective evaluation of the Idylla system compared to other methods, such as other PCR tests, immunohistochemistry, pyrosequencing, sanger sequencing and next generation sequencing. One of these studies (Janku et al., 2015) reported that the operators were blinded to the reference standard/other method results. Overall, the studies concluded that there was good agreement between the Idylla assay and other methods, and included diagnostic outcomes.

The final study (Serre et al., 2018) aimed to evaluate the impact of faster determination of BRAF status. A prospective cohort of samples tested for BRAF mutational status using the Idylla system was compared to a retrospective cohort tested through standard procedures. The authors concluded that use of the rapid Idylla system significantly reduced the time to initiation of personalised treatment compared to standard practice.

Economic evidence

One economic study was identified that explores implementing Idylla platforms (for multiple assays) compared to next generation sequencing, from a French healthcare perspective (Le Flahec et al. 2017). No other economic evidence was identified

Ongoing evidence

No ongoing evidence was identified.

Areas of uncertainty

The evidence identified was for the Idylla rapid fully-automated PCR platform. At this stage it is unknown whether there are similar rapid fully-automated platforms available in the UK.

One of the studies identified compared analysis of cell-free plasma DNA samples and formalin-fixed paraffin-embedded (FFPE) tumor samples. It is unclear whether concordance data for cell-free plasma DNA samples would be appropriate to include in a fuller appraisal when this may not be used in standard practice.

The topic proposer states that Idylla would be an additional step to support rapid oncological decision making; full next generation sequencing would still be done downstream. It is not fully clear whether this is the extent of current provision, or whether other PCR testing is currently available as an interim to the next generation sequencing from the specialised laboratories.

Conclusions

Some primary studies were identified that evaluated the Idylla assay for BRAF mutational status, including one study that aimed to evaluate the impact of incorporating rapid testing into practice. A fuller evaluation of the literature would be required to understand the quality and appropriateness of the evidence identified.

Brief literature search results

Resource	Results
HTA organisations	
Healthcare Improvement Scotland	We did not identify any relevant evidence from this source.
Health Technology Assessment Group	Skin/melanoma chemotherapy regimens: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/melanoma/ Does not refer to specific products for BRAF testing but outlines treatment regimen based on BRAF mutational status. Systemic anti-cancer therapy of patients with metastatic melanoma (2017). Evidence into practice – a rapid review. https://www.hse.ie/eng/services/list/5/cancer/profinfo/guidelines/eiprr%20melanoma.pdf Does not refer to specific products for BRAF testing but includes recommendations based on BRAF mutational status.
Health Information and Quality Authority	We did not identify any relevant evidence from this source.
UK guidelines and guidance	
SIGN	SIGN146 Melanoma. https://www.sign.ac.uk/sign-146-melanoma Does not refer to specific products for BRAF testing, but recommends as best practice that BRAF status should be requested in all patients with advanced disease and recorded on the pathology report. *(Recommended best practice based on the clinical experience of the guideline development group)*
NICE	NICE guideline 14: Melanoma: assessment and management (2015). https://www.nice.org.uk/guidance/ng14 Does not refer to specific products for BRAF testing but outlines treatment regimen based on BRAF mutational status.
Secondary literature and economic evaluations	
ECRI	Not searched.
EUnetHTA	We did not identify any relevant evidence from this source.
Cochrane library	We did not identify any relevant evidence from this source.
Medline (Ovid)	We did not identify any relevant evidence from this source.
Primary studies	
Cochrane library	We did not identify any relevant evidence from this source.
Medline	Bisschop C, Ter Elst A, Bosman LJ, et al. (2018). Rapid BRAF mutation tests in patients with advanced melanoma: comparison of immunohistochemistry, Droplet Digital PCR, and the Idylla Mutation Platform. Melanoma Research. 28(2): 96-104. doi: https://dx.doi.org/10.1097/CMR.0000000000000421 Janku F, Claes B, Huang HJ, et al. (2015). BRAF mutation testing with a rapid, fully integrated molecular diagnostics system. Oncotarget. 6(29): 26886-94. doi: https://dx.doi.org/10.18632/oncotarget.4723

	Janku F, Huang HJ, Claes B, et al. (2016). BRAF Mutation Testing in Cell-Free DNA from the Plasma of Patients with Advanced Cancers Using a Rapid, Automated Molecular Diagnostics System. Molecular Cancer Therapeutics. 15(6): 1397-404. doi: https://dx.doi.org/10.1158/1535-7163.MCT-15-0712 Melchior L, Grauslund M, Bellosillo B, et al. (2015). Multi-center evaluation of the novel fully-automated PCR-based Idylla TM BRAF Mutation Test on formalin-fixed paraffin-embedded tissue of malignant melanoma. Experimental & Molecular Pathology. 99(3): 485-91. doi: https://dx.doi.org/10.1016/j.yexmp.2015.09.004 Schiefer AI, Parlow L, Gabler L, et al. (2016). Multicenter Evaluation of a Novel Automated Rapid Detection System of BRAF Status in Formalin-Fixed, Paraffin-Embedded Tissues. Journal of Molecular Diagnostics. 18(3): 370-7. doi: https://dx.doi.org/10.1016/j.jmoldx.2015.12.005 Van Haele M, Vander Borght S, Ceulemans A, et al. (2020). Rapid clinical mutational testing of KRAS, BRAF and EGFR: a prospective comparative analysis of the Idylla technique with high-throughput next-generation sequencing. Journal of Clinical Pathology. 73(1): 35-41. doi: https://dx.doi.org/10.1136/jclinpath-2019-205970
Ongoing primary or secondary research	
PROSPERO database	We did not identify any relevant evidence from this source.
Clinicaltrials.gov	We did not identify any relevant evidence from this source.
Other	
Additional evidence identified from topic submission	Serre D, Salleron J, Husson M, et al. (2018). Accelerated BRAF mutation analysis using a fully automated PCR platform improves the management of patients with metastatic melanoma. Oncotarget. 9(63): 32232-7. doi: http://dx.doi.org/10.18632/oncotarget.25957 Le Flahec G, Guibourg B, Marcorelles P, et al. (2017). Financial implications of Idylla testing in colorectal cancer, lung cancer and melanoma: a French laboratory point of view. Journal of Clinical Pathology. 70(10): 906. doi: http://dx.doi.org/10.1136/jclinpath-2017-204579

Date of search:	April 2020
Concepts used:	Idylla, rapid PCR test, automated PCR test, BRAF, melanoma