

# Quality and Productivity: Proven Case Study

## BRAFV600E mutation testing for thyroid cancer: avoiding unnecessary surgery

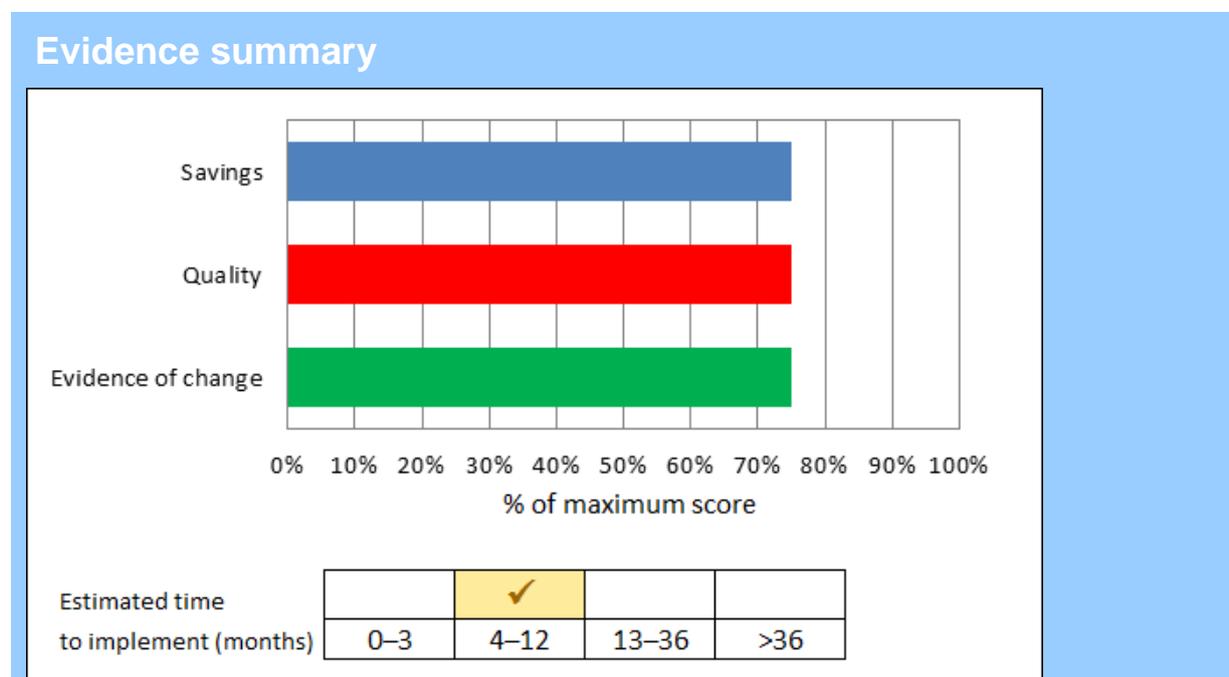
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### Sharing good practice: What are 'Proven Quality and Productivity' case studies?

The NICE Quality and Productivity collection provides users with practical case studies that address the quality and productivity challenge in health and social care. All examples submitted are evaluated by NICE. This evaluation is based on the degree to which the initiative meets the Quality and Productivity criteria: savings, quality, evidence and implementability. The assessment of the degree to which this particular case study meets the criteria is represented in the summary graphic below.

Proven Quality and Productivity examples are case studies that show evidence of implementation and can demonstrate efficiency savings and improvements in quality.



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## Details of initiative

<b>Purpose</b>	To reduce the number of surgical procedures for patients with suspected thyroid cancer by using a mutation test to support the diagnosis.
<b>Description (including scope)</b>	<p>Patients may have surgery to remove all or part of their thyroid gland if cytological examination results suggest they have thyroid cancer.</p> <p>Cytological examination involves a technique called fine needle aspiration to obtain a sample that is then examined under a microscope to detect cells that might be cancerous.</p> <p>A major limitation of thyroid cytological examination is that it cannot always distinguish between benign and malignant neoplasms. If the results indicate a possible cancer but are not conclusive, it is common practice to surgically remove the affected lobe of the thyroid for pathological microscopic examination. This leaves the rest of the thyroid intact. If subsequent tests indicate cancer, a second operation is performed to remove the remaining thyroid gland.</p> <p>In this initiative, when the cytological examination suggests cancer, a mutation test for the BRAF V600E mutation is performed using a commercially available testing kit. The protocol was adapted for use on fine needle aspirate (FNA) samples by using air dried and alcohol fixed FNA cytology smears, rather than formalin fixed paraffin embedded cell blocks. The actual mutation test was unchanged. The method was validated through a blind re-test of samples tested under the previous method. The results were in agreement, indicating a valid method.</p> <p>The BRAF V600E mutation test is more than 99% specific for thyroid cancer, so a positive result means that it is more than 99% likely that the patient has a malignancy and the entire thyroid can be removed in 1 operation rather than 2. This reduces the risks of complications and shortens the total time spent in hospital and recovery.</p> <p>Fifty-seven fine needle aspiration samples were tested between May 2013 and September 2014 and 11 completion thyroidectomies were avoided. The money saved from avoiding the operations outweighs the costs of BRAF V600E testing. Whilst the overall saving is modest, there are significant benefits to patient care.</p>
<b>Topic</b>	Right care, clinical support rationalisation (pathology), safe care, primary care commissioning and contracting.
<b>Other information</b>	BRAF V600E mutations rarely occur in benign thyroid nodules, with a documented frequency in published literature of less than

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1% (Moon et al. 2010), so a positive BRAF V600E result is strongly indicative of cancer. Although the test is highly specific, it is not sensitive enough to be used on its own to diagnose cancer and must be used alongside normal cytological testing. This combined approach provides a specificity of over 99% and a sensitivity of 79% (Koh et al. 2013).

The cost of the test (£300 for an individual test) means it is only economical to test samples from patients in whom cancer is already suspected based on routine cytological testing. Using the Royal College of Pathologists classification system, eligible samples were those classified as Thy4 (suspected malignancy); Thy5 (malignancy); and higher risk Thy3F (possible follicular neoplasm).

## Savings delivered

<b>Amount of savings delivered</b>	<p>Over a 17 month period savings of £15,603 based on national reference costs were achieved for the population of 1 million covered by the tertiary centre. This is equivalent to £1560 per 100,000 population.</p> <p>The savings result from avoiding 11 unnecessary completion thyroidectomies, each saving £2973. This gives a gross saving of £32,703. In total 57 out of 360 samples were sent for BRAF V600 E testing, based on cytological examinations that indicated a possible malignancy. The cost of BRAF V600E testing was £300 per sample, at a gross cost of £17,100. The net saving is therefore £15,603.</p>
<b>Type of saving</b>	<p>Cash savings for the commissioner, from the reduced number of surgical procedures through using a mutation test to support the diagnosis.</p>
<b>Any costs required to achieve the savings</b>	<p>There are no costs of change highlighted. BRAF V600E testing is now widely available because it is part of the work-up for metastatic malignant melanoma when selecting anti-tyrosine kinase inhibitor drugs for patients with metastatic malignant melanoma.</p>
<b>Programme budget</b>	<p>Cancers and tumours; endocrine, nutritional and metabolic problems.</p>
<b>Supporting evidence</b>	<p>Between May 2013 and September 2014, 11 completion thyroidectomies were avoided after 57 samples were tested (Harvey et al. 2014; unpublished data).</p>

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## Quality outcomes delivered

<b>Impact on quality of care or population health</b>	Quality in terms of health outcomes may be improved slightly because of faster diagnosis and treatment, reducing the risk of cancer spreading. This has not been proven however. The main benefits of having 1 operation instead of 2 relate to safety and the patient experience.
<b>Impact on patients, people who use services and/or population safety</b>	Patient safety is improved overall because for affected patients only 1 operation under general anaesthesia is performed instead of 2, reducing the risk of complications.
<b>Impact on patients, people who use services, carers, public and/or population experience</b>	The patient experience is improved significantly because affected patients will have their surgery done in one procedure, avoiding a second operation, hospital stay and recovery.
<b>Supporting evidence</b>	Between May 2013 and September 2014, 11 completion thyroidectomies were avoided after 57 samples were tested (Harvey et al. 2014; unpublished data).

## Evidence of effectiveness

<b>Evidence base for case study</b>	Underpinned by peer-reviewed scientific evidence on the accuracy of the test for the mutation (Koh et al. 2013; Poller and Glaysher 2013; Rossi et al. 2013; Johnson et al. 2014).
<b>Evidence of deliverables from implementation</b>	<p>The initiative has been implemented locally with systematic reporting of results.</p> <p>Of the 360 fine needle aspirations performed between May 2013 and September 2014, 57 specimens underwent BRAF V600E testing. Of those, 16 (28%) showed evidence of BRAF V600E mutation and were managed as malignancies. Five of these were Thy5 cases included for quality control purposes and would have had a total thyroidectomy in any case. Eleven completion thyroidectomies were avoided however, with patients receiving a total thyroidectomy as a result of the BRAF V600E test and subsequent multidisciplinary team discussions. Overall this means that for roughly every 6 BRAF V600E tests performed, 1 completion thyroidectomy was avoided.</p>
<b>Where implemented</b>	Portsmouth Acute Hospitals NHS Trust.
<b>Degree to which the</b>	The initiative met expectations.

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**actual benefits  
matched  
assumptions**

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**If initiative has been  
replicated how  
frequently/widely has  
it been replicated**

The system is used widely outside the UK and is common practice in America (Ferris et al. 2015) and Australia (Royal College of Pathologists of Australia 2014).

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**Supporting evidence**

The technique is supported by peer-reviewed evidence (Koh et al. 2013; Poller and Glaysher 2013; Rossi et al. 2013; Johnson et al. 2014).

Data from implementation of the initiative provided in Poller et al. (2014) with additional information provided in a PowerPoint presentation discussing the results, updated to September 2014 (Harvey et al. 2014; unpublished data).

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## Details of implementation

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**Implementation  
details**

Portsmouth Acute Hospitals NHS Trust is a large tertiary cancer referral centre in the southern part of the UK with a patient catchment population approaching 1 million. Cases of suspected thyroid cancer are managed by the Portsmouth and Southeast Hampshire thyroid multidisciplinary team.

The multidisciplinary team reviewed the published evidence around testing of fine needle aspiration samples for the BRAF V600E mutation. It was decided that samples would have BRAF V600E testing if malignancy was suspected but there was some uncertainty based on cytological examination. Those testing positive would then be managed as malignancies.

The samples tested were mostly those classed as Thy4 (suspected malignancy, n=17) using the Royal College of Pathologists classification system, but also some higher risk Thy3F (neoplasm possible, n=30) and some Thy5 (malignant, n=8) samples where there was diagnostic uncertainty. In addition, 1 Thy3a sample (lower risk for possible neoplasm) was sent for testing because of the pathologist's concerns about the sample, and 1 sample was sent for testing but did not yield sufficient material. The reason for testing some Thy 5 cases as well as Thy 4 and Thy 3F cases is that there is a small false positive rate with Thy 5 (less than 1%) for cancer on thyroid FNA.

In total 360 fine needle aspirations were received by the laboratory between May 2013 and September 2014. Of these, 57 (16%) were sent for BRAF testing, with a note added to the cytology reports to indicate a BRAFV600E test result was pending. Selection criteria were the Thy3F, Thy4 or Thy5

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classifications previously described, as well as the availability of at least 2 slides from a patient that indicated abnormal cells. This is because the BRAF V600E test sacrifices the cells used for DNA extraction and so at least 1 slide must be preserved for medico-legal purposes and also for discussion by the multidisciplinary team to plan treatment. Therefore in some cases there was insufficient material to perform the BRAF V600E test and those cases were managed with a lobectomy as in the old pathway.

BRAF V600E testing was performed fortnightly or weekly as required. For the 57 samples tested, a commercially available kit was used, allowing the use of air-dried and alcohol-fixed cytology smears (for technical details see Poller et al. 2014). The results of the test were issued in a supplementary report, attached to the original cytology report, for discussion by the multidisciplinary team.

Cases with the BRAF V600E mutation were managed as definite malignancies, and the patients were offered a total thyroidectomy. If the BRAFV600E test was negative then a lobectomy was offered, as the low sensitivity of the BRAF V600E for cancer means that a negative result does not guarantee that there is not a cancer present. Samples from the subsequent lobectomies underwent histopathological examination to determine if there was malignancy.

<b>Time taken to implement</b>	Can be achieved in less than a year, because of the commercial availability of the required kits, but may require some training. This should not be a major cost because BRAF V600E testing is now part of the work-up for metastatic malignant melanoma when selecting anti-tyrosine kinase inhibitor drugs for patients with metastatic malignant melanoma. Wider agreement on the pathway change may also be required before implementation.
<b>Ease of implementation</b>	Affects a whole organisation across a number of teams or departments. Involves changes in diagnostic testing and ultimately surgery as the balance shifts towards single thyroidectomies.
<b>Level of support and commitment</b>	Likely to achieve good buy in from key influencers.
<b>Barriers to implementation</b>	BRAF V600E testing is now widely available, but if expertise and equipment is not available locally then samples may need to be sent to a specialist centre.
<b>Risks</b>	Individuals' treatment preferences and clinical circumstances may vary. It is essential that all cases are discussed by a multidisciplinary team to ensure appropriate management on a case-by-case basis. Management decisions should not be based

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on the result of the BRAF V600E test, or any other test, alone.

The BRAF V600E test should not be performed if only 1 slide showing abnormal cells is available, because a slide is also required for discussion by the multidisciplinary team. Sampling protocols could be changed to take additional samples for mutation testing, but this has not been needed so far.

Management should not be delayed unnecessarily because of delays in BRAF V600E testing; in this initiative the maximum waiting time between sample collection and testing was 2 weeks.

Around 0.5% of thyroid tumours are metastatic tumours to the thyroid. Metastatic tumours such as BRAF V600E mutated malignant melanoma are rare but do occur. BRAFV600E mutated metastatic adenocarcinomas to the thyroid also occur e.g. from lung and colorectum. BRAF V600E testing for the diagnosis of primary thyroid carcinoma should always be undertaken in the clinical context and with full MDT discussion of all the relevant clinical information, previous medical history, imaging findings, and pathological data.

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## Supporting evidence

A detailed description of implementation was provided, with results from unpublished data. Please see the section 'Evidence of effectiveness' for details.

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## Further evidence

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### Dependencies

A multidisciplinary team for the management of thyroid cancer and a laboratory with the equipment and staff to conduct the required tests are required.

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## Contacts and resources

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### Contacts and resources

If you require any further information please email: [qualityandproductivity@nice.org.uk](mailto:qualityandproductivity@nice.org.uk) and we will forward your enquiry and contact details to the provider of this case study. Please quote reference 13/0007 in your email.

Ferris RL, Baloch Z, Bernet V et al. (2015) American Thyroid Association statement on surgical application of molecular profiling for thyroid nodules: current impact on perioperative decision making. *Thyroid* 25: 760–8

Harvey KL, Glaysher S, Agrawal A et al. (2014) BRAF V600 co-testing in thyroid FNA cytology: short-term experience in a large cancer centre in the UK [PowerPoint presentation; unpublished]

Johnson SJ, Hardy SA, Roberts C et al. (2014) Pilot of BRAF mutation analysis in indeterminate, suspicious and malignant

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thyroid FNA cytology. *Cytopathology* 25: 146–54

Koh J, Choi JR, Han KH et al. (2013) Proper indication of BRAFV600E mutation testing in fine-needle aspirates of thyroid nodules. *PLoS ONE* 8: e64505

Moon HJ, Kim EK, Chung WY et al. (2010) Diagnostic value of BRAF(V600E) mutation analysis of thyroid nodules according to ultrasonographic features and the time of aspiration. *Annals of Surgical Oncology* 18: 792–9

Poller DN, Glaysher S (2013) BRAF V600 co-testing is technically feasible in conventional thyroid fine needle aspiration (FNA) cytology smears and can reduce the need for completion thyroidectomy. *Cytopathology* 25: 155–9

Poller DN, Glaysher SG, Agrawal A et al. (2014) BRAF V600 co-testing in thyroid FNA cytology: short-term experience in a large cancer centre in the UK. *Journal of Clinical Pathology* 67: 684–9

Poller DN, Kandaswamy P (2013) A simplified economic approach to thyroid FNA cytology and surgical intervention in thyroid nodules. *Journal of Clinical Pathology* 66: 583–8

Rossi ED, Martini M, Capodimonti S et al. (2013) Diagnostic and prognostic value of immunocytochemistry and BRAF mutation analysis on liquid-based biopsies of thyroid neoplasms suspicious for carcinoma. *European Journal of Endocrinology* 168: 853–9

Royal College of Pathologists of Australia (2014) Thyroid cytology structured reporting protocol. RCPA, Surry Hills

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