# Lung Cancer Research Review™

Making Education Easy

Issue 7 – 2016


## In this issue:



**Abbreviations used in this issue**

**ALK** = anaplastic lymphoma kinase
**DFS** = disease-free survival
**EGFR** = epidermal growth factor receptor
**EGFR-TKI** = epidermal growth factor receptor-tyrosine kinase inhibitor
**NSCLC** = non-small cell lung cancer
**OS** = overall survival
**PFS** = progression-free survival


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# Welcome to the seventh issue of Lung Cancer Research Review.

Highlights in this issue include results from the RADIANT study and investigations into targeted therapies for and histological subtyping of lung adenocarcinoma. Other highlights include associations between pulmonary diseases and lung cancer and the effects of lung cancer screening on patient attitudes to smoking cessation.

With this issue we welcome Greg Frazer as one of our two Medical Expert Reviewers. Greg takes over commentary duties from Chris Lewis who has been with us since the first issue of Lung Cancer Review. We sincerely thank Chris for his thorough, thoughtful, and clinically-savvy contributions over the first six issues.

We hope that you enjoy this issue of Lung Cancer Research Review. As ever, we look forward to receiving your comments and feedback.

Kind regards,


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## Intratumoral heterogeneity of ALK-rearranged and ALK/EGFR coaltered lung adenocarcinoma

**Authors:** Cai W et al.


**Summary:** The aim of this study was to investigate the potential effect of intra-tumoral heterogeneity on both genetic and pathologic characteristics of ALK-rearranged lung adenocarcinoma (LADC). The researchers tested for ALK fusions and EGFR mutations in the primary tumours of patients with LADC using laser-capture microdissection. Of 629 patients tested, 30 (4.8%) had ALK fusions, 364 (57.9%) had EGFR mutations, and two had ALK fusions that co-existed with EGFR mutations. Intra-tumoral heterogeneity of ALK fusions were identified in nine patients. Genetic intra-tumoral heterogeneity was observed in two patients with an ALK/EGFR co-altered status. In an expanded statistical analysis of 900 individual adenocarcinoma components, ALK fusions were positively associated with a micro-papillary pattern (p=0.002) and were negatively associated with a lepidic pattern (p=0.008).


**Comment (GL):** For those patients with suitable lesions, targeted therapies have been a real improvement in advanced adenocarcinoma of the lung. At the turn of the millennium, the best available chemotherapy could still offer a median survival of less than a year. Targeted treatments for patients with EGFR sensitising mutations and ALK gene rearrangements now offer median survivals approaching two years. In New Zealand, the first generation EGFR-targeting agents gefitinib and erlotinib are funded, but there is no funded ALK drug.

The trouble is that these medicines still fail. This study reveals genetic and morphological variability within tumours that may underlie treatment failure. It is a depressing prospect that our most effective drugs seem to at best delay the Darwinian selection of resistant tumour clones. But this is information that we need to know, in order to guide the next slow steps of clinical research. My own inclination is to be more sceptical of the claims of "precision medicine" and more in favour of an immunological "scattergun".


***Reference: J Clin Oncol 2015;33(32):3701–9***
Abstract


### Independent commentary by Dr George Laking MD PhD FRACP

George is a Medical Oncologist at Auckland DHB, specialising in treatment of respiratory malignancy. Outside the DHB George is also active as a member of PTAC (Pharmac's Pharmacology and Therapeutics Advisory Committee), and the Smokefree Coalition. **FOR FULL BIO CLICK HERE.**

### Independent commentary by Dr Greg Frazer

Greg is Clinical Director of the Respiratory Department at Christchurch Hospital and is a member of the National Lung Cancer Working Group. He is a Fellow of the Royal Australian College of Physicians.
**FOR FULL BIO CLICK HERE.**

Time spent reading this publication has been approved for CME for Royal New Zealand College of General Practitioners (RNZCGP) General Practice Educational Programme Stage 2 (GPEP2) and the Maintenance of Professional Standards (MOPS) purposes, provided that a Learning Reflection Form is completed. Please **CLICK HERE** to download your CPD MOPS Learning Reflection Form. One form per review read would be required.

Time spent reading this publication has been approved for CNE by The College of Nurses Aotearoa (NZ) for RNs and NPs. For more information on how to claim CNE hours please **CLICK HERE**.

## Adjuvant erlotinib versus placebo in patients with stage IB-IIIA non-small-cell lung cancer (RADIANT): A randomized, double-blind, phase III trial

**Authors:** Kelly K et al.

**Summary:** This international, randomised, double-blind, placebo-controlled study assessed the efficacy of adjuvant erlotinib in patients with completely resected IB to IIIA NSCLC whose tumours expressed EGFR protein. A total of 973 patients were randomly assigned (2:1) to receive erlotinib 150mg once daily or placebo for 2 years. There was no statistically significant difference in DFS (median, 50.5 months for erlotinib vs 48.2 months for placebo; HR, 0.90; 95% CI, 0.74–1.10; p=0.324). Among the 161 patients (16.5%) in the EGFRm-positive subgroup, DFS favoured erlotinib (median, 46.4 vs 28.5 months; HR, 0.61; 95% CI, 0.38–0.98; p=0.039); however, this was not statistically significant because of the hierarchical testing procedure. Rash (22.3%) and diarrhoea (6.2%) were the most common grade 3 adverse events in patients treated with erlotinib.

**Comment (GL):** Nowadays it is understood that EGFR-targeting in NSCLC is relevant only to the subset of patients with EGFR-mutant lesions. Erlotinib, however, had a longer run of development in all-comers, i.e., both patients with EGFR wild-type and EGFR mutations. In fact, only in 2015 did erlotinib's manufacturer step back from its marketing in EGFR wild-type. The RADIANT trial is a legacy of this time in which it seemed that erlotinib might be relevant to all NSCLC. The answer, so far as it relates to two years of adjuvant treatment, is a negative. The interesting results are for the subset with EGFR mutations. The authors are correct to point out that these may simply have reflected the play of chance. But look at the Kaplan-Meier curve in figure 2b. Progression-free survival hits a wall just short of four years. It makes me think that the best that small molecule adjuvant EGFR targeting can do in this illness is delay relapse, rather than cure.

***Reference: J Clin Oncol 2015;33(34):4007–14***
Abstract

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**Disclaimer:** This publication is not intended as a replacement for regular medical education but to assist in the process. The reviews are a summarised interpretation of the published study and reflect the opinion of the writer rather than those of the research group or scientific journal. It is suggested readers review the full trial data before forming a final conclusion on its merits.

**Research Review publications are intended for New Zealand health professionals.**

## Is it safe to wait? The effect of surgical wait time on survival in patients with non-small cell lung cancer

**Authors:** Coughlin S et al.

**Summary:** The objective of this study was to determine the effect of surgical wait time on survival and incidence of upstaging in patients with stage I and II NSCLC who underwent surgical resection. For stage I patients (n=180), wait times of ≤4 months had no significant effect on survival or incidence of upstaging. For stage II patients (n=42), those waiting 2–3 months had significantly decreased survival (HR 3.6, p=0.036) and increased incidence of upstaging (OR 2.0, p=0.020) than those waiting 0–1 month.

**Comment (GF):** The diagnosis of lung cancer is extremely distressing, even for those patients with early disease who are offered curative-intent treatment. For this group, one of the major concerns is that any delay before receiving treatment will result in disease progression and decreased survival — this concern has been shown to have a negative impact on quality of life. There is, however, little evidence on the impact of increased wait times on survival, at least for resection, and current wait time targets are largely based on consensus expert opinion.

This study, from Ontario in Canada, examined the impact of wait time to surgery on survival in a cohort of 222 patients from a single surgical centre. Unsurprisingly, the majority of patients (81%) in the study had clinical stage I disease, with the remainder having stage II disease. Only 22% of stage I and 38% of stage II patients were operated on within the target time, which in Ontario is within 28 days of a decision to treat. The authors found though that wait time did not affect survival in stage I patients, nor did it impact on the incidence of upstaging. For the patients with clinical stage II disease, however, wait time of >2 months did result in a significant decrease in survival in stage II patients when compared to those who were operated on within 1 month. The incidence of upstaging was also increased in those waiting >2 months. Tumour histology was not significantly associated with survival or upstaging in the stage I group, this was not specifically addressed in the stage II group.

There are some limitations to the study that need to be recognised, including the relatively small sample size and the fact that a relatively small proportion of patients had invasive mediastinal staging prior to resection. The two groups were also not further subdivided into stage IA/ IB and stage IIA/ stage IIB. Nevertheless, these results can provide some reassurance to patients with stage I disease that a longer wait to surgery is unlikely to have an adverse effect on their outcome. The authors conclude that patients with clinical stage II disease be prioritised for more timely treatment, and suggest that broad recommendations for surgical wait times across all stages may be inappropriate. How this sits within our Faster Cancer Treatment framework remains to be seen!

***Reference: Can J Surg 2015;58(6):414–418***
Abstract

## Comparison of skin toxic effects associated with gefitinib, erlotinib, or afatinib treatment for non-small cell lung cancer

**Authors:** Chen KL et al.

**Summary:** EGFR-TKIs have been widely used to treat NSCLC. This retrospective study directly compared the incidences and severities of four types of skin toxicities for three different EGFR-TKIs in the same patient cohort.

**Comment (GL):** Gefitinib and erlotinib are New Zealand's two publicly-funded first-generation EGFR-TKIs. Afatinib is a second-generation EGFR-TKI registered but not funded in this country. It is indicated for treatment of TKI-naïve tumours with EGFR exon 19 deletions or exon 21 (L858R substitution) mutations. Noting that these drugs target the EGFR, it is not a surprise that they have cutaneous toxicities. The mainstays of supportive care are cetomacrogol moisturising creams and lotions, and occasional antibiotics for acne and folliculitis. Up to a point, patients can be reassured by evidence that skin toxicity predicts the drug will work.
Although the authors report a higher incidence of skin toxicity with afatinib in the first six months, this is a retrospective non-randomised study design. The finding of a reduction in dermatological visits for all three drugs after the first six months would fit with clinical observations of "tachyphylaxis", or patients learning to manage toxicities behaviourally and physiologically. More pessimistically, it is also possible that some of the patients gave up either the treatment or their dermatologist.

***Reference: JAMA Dermatol 2015 Dec 9:1–3. [Epub ahead of print]***
Abstract

## Postoperative radiation therapy is associated with improved overall survival in incompletely resected stage II and III non-small-cell lung cancer

**Authors:** Wang EH et al.

**Summary:** These investigators reviewed trends in the use of post-operative radiotherapy (PORT) for pathologic NO-2 stage II and III incompletely resected NSCLC and evaluated the association between PORT and survival in such patients (who were identified within the National Cancer Data Base). Only patients coded as receiving external-beam PORT at 50–74 Gy or observation were included in the analysis. Of 3,395 patients identified, 1,207 (35.6%) received PORT. Predictors for the use of PORT in this patient population included: age <60 years, treatment in a non-academic facility, earlier year of diagnosis, decreased travel distance, lower nodal stage, and treatment with chemotherapy. On multivariable analysis adjusting for demographic and clinic-pathologic covariates, PORT (HR, 0.80; 95% CI, 0.70–092) was associated with improved survival.

**Comment (GL):** Radiotherapy improves survival in patients with unresected locally-advanced (nodal stages N2 and N3) NSCLC. Radiotherapy is, however, toxic to normal tissues, in particular the lung. There is evidence that post-operative radiotherapy actively reduces survival after complete resection of N0 and N1 lung cancer. At what stage of disease does harm cross over to benefit? This study asks the question for patients who had R1 (microscopic positive) and R2 (macroscopic positive) margins after resection of N0 to N2 NSCLC. The authors deploy statistical wizardry on the non-randomised US National Cancer Data Base and find a hazard ratio of 0.80 in favour of PORT at 50–74 Gy. We cannot expect to see a randomised trial on the topic. The argument looks convincing to this Medical Oncologist. Research Review welcomes correspondence.

***Reference: J Clin Oncol 2015;33(25):2727–34***
Abstract

## Interpreting small treatment differences from quality of life data in cancer trials: an alternative measure of treatment benefit and effect size for the EORTC-QLQ-C30

**Authors:** Khan J et al.

**Summary:** These researchers analysed HRQoL (EORTC-QLQ-C30) data from six randomized controlled lung cancer trials (two small cell and four in non-small cell) involving a total of 2909 patients and determined preferences for odds ratios (ORs) versus mean differences (MDs). HRQoL effects using ORs offered coherent interpretations: MDs >0 resulted in ORs >1 and vice versa; effect sizes were classified as 'trivial' if the OR was between 0.95 and 1.05; 'small' if between 0.9 and 1.1; 'medium' if between 0.8 and 1.2; and 'large' if <0.8 or >1.20. Small HRQoL effects on the MD scale appeared to translate to important treatment differences on the OR scale. Conversely, small ORs were unlikely to yield large MDs. Oncologists appeared to prefer ORs over MDs since interpretation is similar to HRs.

**Comment (GL):** It is hard to be enthusiastic about this project on small differences in quality of life data. The basic issue is there in the title: a treatment was associated with a small difference in quality of life. If your statistical problem is that you want to make a difference look larger, then pick an OR — it departs further from unity than a relative risk. The authors do offer an illuminating Example 5: the study in which patients had less total burden of diarrhoea symptoms (negative mean difference) but were more likely to have diarrhoea (OR exceeded unity). This project illustrates two differing purposes to which quality of life data are used. Both purposes are legitimate. Health economists want to know about mean differences, because they use these to construct quality-adjusted life-years. Clinician scientists want to know about the distribution of symptoms within a population, because they need to improve their treatments. As a clinician there is always the concern that a small mean difference in effect may conceal widely divergent experiences of treatment — that is not something we can let go past.

***Reference: Health Qual Life Outcomes 2015;13:180***
Abstract

## The effects of pulmonary diseases on histologic types of lung cancer in both sexes: a population-based study in Taiwan

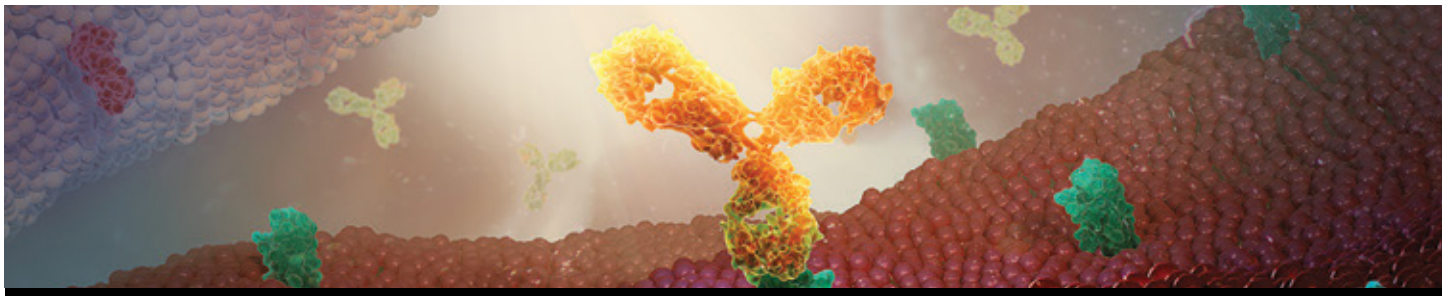
**Authors:** Huang JY et al.

**Summary:** The aim of this study was to assess whether pulmonary diseases are associated with an increased risk of specific types of lung cancer. Patients newly diagnosed with lung cancer were identified from the National Health Insurance Research Database in Taiwan. Histologic types of lung cancer were further confirmed using the Taiwan Cancer Registry Database. A total of 32,759 cases of lung cancer were identified from 15,219,024 insurants aged ≥20 years. In men and women, respectively, the adjusted HR estimates of squamous cell carcinoma were 1.37 (95% CI, 1.21–1.54) and 2.10 (95% CI, 1.36–3.23) for Tb, 1.52 (95% CI, 1.42–1.64) and 1.50 (95% CI, 1.21–1.85) for asthma, and 1.66 (95% CI, 1.56–1.76) and 1.44 (95% CI, 1.19–1.74) for COPD. Similarly, the adjusted HR estimates of adenocarcinoma were 1.33 (95% CI, 1.19–1.50) and 1.86 (95% CI, 1.57–2.19) for Tb, 1.13 (95% CI, 1.05–1.21) and 1.18 (95% CI, 1.09–1.28) for asthma, and 1.50 (95% CI, 1.42–1.59) and 1.33 (95% CI, 1.25–1.42) for COPD. The HRs of small cell carcinoma were also reported.

**Comment (GF):** Cigarette smoking remains the major risk factor for developing lung cancer, but chronic inflammation has also been implicated in lung carcinogenesis. This extensive review from Taiwan using National Health Insurance and lung cancer registry data examines the associations between lung cancer and pulmonary disease, and also sought to determine whether there was an association with any specific histological subtype.

Patients with lung cancer had higher rates of asthma, COPD, Tb, hyperlipidaemia, diabetes, chronic kidney disease, and other smoking-related cancers than individuals without lung cancer did. Asthma, COPD, and Tb were associated with an increased risk of all major subtypes of lung cancer, with the risk being highest amongst women with a history of Tb. The biggest strength of this paper is its comprehensiveness; Taiwan's National Health Insurance programme covers more than 99% of the population so almost all cases of lung cancer in the country were able to be analysed. The Taiwanese population is relatively homogeneous, so these results might not be able to be extrapolated to other settings; having said that, studies amongst other populations have shown similar findings. Other lung diseases, notably interstitial lung disease, have also been shown to have an association with lung cancer. The results reinforce the importance of considering pulmonary disease in the pathogenesis of lung cancer, so would also support the concept of adequate treatment of these conditions to reduce chronic inflammation and subsequent carcinogenic potential.

***Reference: BMC Cancer 2015 Nov 2;15:834***
Abstract



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## Early results from the implementation of a lung cancer screening program: The Beaumont Health System experience

**Authors:** Lanni TB Jr et al.

**Summary:** These investigators compared the outcomes and costs associated with developing and implementing a lung cancer screening programme. Patients (n=1065) were screened on a low-dose computed tomography (CT) screening protocol and the American College of Radiology Lung Imaging Reporting and Data System (Lung-RADS) were used to score each patient. At 1 year, 20 patients (1.6%) were diagnosed with lung cancer and another 15 patients were diagnosed with another form of cancer after screening. The median age, packs per day, and pack-years smoked for all patients was 63, 1.0, and 39.0 years, respectively. Lung-RADS scores for all patients were 18% (1), 24.1% (2), 6.3% (3), and 5.4% (4).

**Comment (GF):** The results of the National Lung Cancer Screening Trial (NLST) have, to quote the authors of this study "provided the momentum to change the paradigm for which early detection for lung cancer will be conducted". Screening of selected patients has been recommended by a number of professional bodies, in North America at least, and will be covered by Medicare/Medicaid. A number of programmes are now established in the US, and this paper reviews early results from one of them, the Beaumont Health System in Michigan.

A total of 1065 patients were screened over a one-year period (January to December 2015), resulting in the detection of 20 lung cancers and 15 patients with other forms of lung cancer — results were thought to parallel the detection rate in the CT arm of the NLST. There was also a net revenue of US$3.2 million from the first year of screening, equating to US$3100 per patient (although direct and additional costs were not calculated). The (self-evident) conclusion was that the establishment of a screening programme improved the ability to screen patients, and improved compliance with evidence-based guidelines and follow up. Lung cancer screening with low-dose CT is here to stay, and this paper, amongst others, describes the introduction of programmes within the real world rather than in a clinical trial setting. Whilst the authors clearly feel that their screening programme has been successful, both in terms of improvement in the detection of early cancers and in generating revenue for their health system, there are a number of unanswered questions. They do identify some limitations and concerns, including co-ordination of care for patients who are found to have nodules or develop lung cancer. There was, however, no information provided about what proportion of patients within their health system who met screening criteria actually received it, which in my opinion at least is a more critical determinant of the success of the implementation of a screening programme. It will also be interesting to see how many of the patients return for their second and subsequent screening CTs.

The economic analysis, which is actually rather brief within the body of the paper, is also interesting, but perhaps not particularly relevant in a New Zealand context, where any economic analysis of a proposed screening programme would need to measure affordability rather than potential revenue!

***Reference: Am J Clin Oncol 2015 Dec 8. [Epub ahead of print]***
Abstract

## Solid predominant histologic subtype in resected stage I lung adenocarcinoma is an independent predictor of early, extrathoracic, multisite recurrence and of poor postrecurrence survival

**Authors:** Ujiie H et al.

**Summary:** This study evaluated the significance of the proposed International Association for the Study of Lung Cancer, American Thoracic Society, and European Respiratory Society (IASLC/ATS/ERS) histologic subtypes of lung adenocarcinoma for patterns of recurrence and, among patients who recur following resection of stage I lung adenocarcinoma, for post-recurrence survival (PRS). Of 1,120 patients identified, 188 had recurrent disease, of whom 103 died as a result of lung cancer. Among patients who recurred, 2-year PRS was 45%, and median PRS was 26.1 months. Patients with solid predominant tumours had earlier (p=0.007), more extra-thoracic (p<0 .001), and more multisite (p=0.011) recurrences compared with patients with non-solid tumours. According to multivariable analysis of primary tumour factors, solid predominant histologic pattern in the primary tumour (HR, 1.76; p=0 .016), age >65 years (HR, 1.63; p=0.01), and sublobar resection (HR, 1.6; p=0.01) were significantly associated with worse PRS in patients who recurred.

**Comment (GF):** Adenocarcinoma, the most common type of lung cancer, can now be further classified on the predominant histological subtype present within the tumour, with the five described patterns being lepidic, papillary, acinar, micropapillary, and solid. Lepidic predominant adenocarcinoma in situ is associated with a very good prognosis, whilst invasive adenocarcinoma with micropapillary and solid patterns have been consistently associated with poorer prognosis. The authors of this study sought to determine whether tumour subtype predicted recurrence and post-recurrence survival in patients who had undergone resection for stage I adenocarcinoma.

More than 1100 patients treated over a 10-year period were included in the analysis; 17% had disease recurrence. Predominantly solid tumours were found to have a higher incidence of recurrence than non-solid tumours, and were also found to be unfavourably associated with post-recurrence survival. The authors conclude that there is a rationale to investigate adjuvant therapy and novel therapeutic targets for patients with solid predominant lung adenocarcinoma. A separate article in the same volume of J Clin Oncol examined the predictive value of histological subtype on survival from adjuvant chemotherapy following surgical resection and found that there was a non-significant trend toward overall survival benefit and a significant DFS benefit in the patients with micropapillary or solid tumours compared those with acinar or papillary histology after receiving adjuvant therapy.

As we increasingly move toward personalised medicine and targeted therapy, these papers highlight the importance of histological subtype as well as mutation analysis in determining the most appropriate treatments for patients with lung cancer. Just as there are now promising genetic markers for targeted therapy in squamous carcinoma as well as adenocarcinoma, we can hopefully look forward to improvements in the histological classification of other types of lung cancer that may predict treatment effect.

***Reference: J Clin Oncol 2015;33(26):2877-84***
Abstract

## Attitudes and perceptions about smoking cessation in the context of lung cancer screening

**Authors:** Zeliadt SB et al.

**Summary:** This was an ancillary study to the launch of a lung cancer screening programme at seven sites in which 45 in-depth semi-structured qualitative interviews about health beliefs related to smoking and lung cancer screening were administered by telephone to 37 current smokers offered lung cancer screening by their primary care physician. Lung cancer screening prompted most current smokers to reflect on what smoking means for their current and future health. However, 17 of 35 (49%) respondents described mechanisms whereby screening lowered their motivation to stop smoking. These included the perception that undergoing an imaging test yields the same health benefits as smoking cessation, the belief that screening and being able to return for additional screening offers protection from lung cancer, and the perception by some individuals that findings from screenings have saved their lives by catching their cancer early.

**Comment (GF):** Lung Cancer screening guidelines arising from the National Lung Cancer Screening Trial emphasise the importance of smoking cessation and the need to ensure that patients do not see screening as a substitute for smoking cessation. Reports on smoking cessation rates following lung cancer screening have shown mixed results, but to date there has been little information on how patients receiving screening perceive smoking cessation.

Most of the current smokers in this study did reflect on smoking and its impact on their health. Some were able to stop smoking, so there was some evidence that screening can positively influence behaviours, but nearly half felt that screening may actually reduce their motivation to quit. A number of different mechanisms for this were described, but a common thread was that screening was seen to be protective from lung cancer and so reduced the benefit of quitting. The bottom line is that there are many misconceptions around screening, particularly its perceived protective effect, and that undergoing screening may reduce the perceived need to stop smoking for many patients. Any screening programme that is introduced in New Zealand will need to include not only smoking cessation but also patient education about the limitations and misconceptions of screening.

***Reference: JAMA Intern Med 2015;175(9):1530–7***
Abstract

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