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Utility of incorporating a gene-based lung cancer risk test on uptake and adherence in a community-based lung cancer screening pilot study

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ABSTRACT

Based on the results of randomized control trials, screening for lung cancer using computed tomography (CT) is now widely recommended. However, adherence to screening remains an issue outside the clinical trial setting. This study examines the utility of biomarker-based risk assessment on uptake and subsequent adherence in a community screening study.

In a single arm pilot study, current or former smokers > 50 years old with 20 + pack year history were recruited following local advertising. One hundred and fifty seven participants volunteered to participate in the study that offered an optional gene-based lung cancer risk assessment followed by low-dose CT according to a standardised screening protocol.

All 157 volunteers who attended visit 1 underwent the gene-based risk assessment comprising of a clinical questionnaire and buccal swab. Of this group, 154 subsequently attended for CT screening (98%) and were followed prospectively for a median of 2.7 years. A participant's adherence to screening was influenced by their baseline lung cancer risk category, with overall adherence in those with a positive scan being significantly greater in the "very high" risk group compared to "moderate" and "high" risk categories (71% vs 52%, Odds ratio = 2.27, 95% confidence interval of 1.02–5.05, P = 0.047). Those in the "moderate" risk group were not different to those in the "high" risk group (52% and 52%, P > 0.05).

In this proof-of-concept study, personalised gene-based lung cancer risk assessment was well accepted, associated with a 98% uptake for screening and increased adherence for those in the highest risk group.

1. Introduction

Several randomised control trials (RCT) have now shown that computed tomography (CT) screening improves outcomes in lung cancer screening (Aberle et al., 2011; de Koning et al., 2020; Pastorino et al., 2019). Results from the National Lung Screening Trial (NLST), the first randomised control trial which reported in 2011, found that low-dose CT screening in high-risk smokers reduces lung cancer mortality by 20% above that of screening using chest radiographs (Aberle et al., 2011). The recently reported NELSON trial reported reductions in lung cancer mortality of 24% and 33% in men and women respectively when CT was compared to a usual care control arm (de Koning et al., 2020). Based on the results of the NLST, CT-based screening for lung cancer is now widely recommended in the United States of America (USA) (Jaklitsch et al., 2012; Detterbeck et al., 2013; Humphrey et al., 2013). Despite the growing evidence, uptake of screening in the USA remains very low and in the order of 5–14% of those eligible (Montes et al., 2007; Zahnd and Eberth, 2019; Richards et al., 2020). While there may be many reasons for this low uptake, engagement of high risk smokers remains a challenge (Zahnd and Eberth, 2019; Richards et al., 2020; Fedewa SA, Kazerooni EA, Studts JL, et al. State Variation in Low-dose CT Scanning for Lung Cancer Screening in the United States. J Natl Cancer Inst, 2020; Cattaneo et al., 2018; Hirsch et al., 2019; Tanner et al., 2020; Lopez-Olivo et al., 2020; Patel et al., 2012; Young and Hopkins, 2012; Griffiths et al., 2012; Silvestri et al., 2007; Kim et al., 2008; Schnoll et al., 2003; Hahn et al., 2006).

Several studies have examined patient characteristics underlying a current or former smoker's participation (uptake) in CT-based lung

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cancer screening (Patel et al., 2012; Young and Hopkins, 2012; Griffiths et al., 2012; Silvestri et al., 2007; Kim et al., 2008; Schnoll et al., 2003; Hahn et al., 2006). These studies consistently report that self-perceived risk of lung cancer is one factor determining which current or former smokers participates in screening. This finding is not unique to lung cancer screening but is universally found in all cancer screening programmes (Hahn et al., 2006; McCaul et al., 1996; Bloss et al., 2011). Smokers with the highest risk perception not only have a greater interest in screening for lung cancer, they also have greater participation rates (Silvestri et al., 2007; Kim et al., 2008). This is highly problematic because in the absence of personalised risk assessment, smokers generally underestimate their own risk of lung cancer relative to other smokers (Weinstein et al., 2005). This underestimate of self-perceived risk is termed unrealistic optimism (or optimistic bias) and reflects varying degrees of denial, which together with nicotine addiction, perpetuates the smoking habit. This denial is reinforced by a smoker's lack of motivational tension, a state reflective of their fear of suffering a fatal complication of smoking such as lung cancer (Weinstein et al., 2005). Not surprisingly, the tendency to high levels of unrealistic optimism (denial) and low levels of motivational tension (fear) determines a smoker's interest, and ultimately participating, in risk mitigating activities such as smoking cessation (Nichols et al., 2017; Senft et al., 2019) and CT screening for early detection of lung cancer (Hahn et al., 2006; Weinstein et al., 2005; Young and Hopkins, 2012; Griffiths et al., 2012; Silvestri et al., 2007; Kim et al., 2008). In addition to uptake for lung cancer screening, there has been growing interest in adherence to screening following the baseline scan (Spiro, 2007; Park et al., 2013; Montes et al., 2007; Zahnd and Eberth, 2019; Richards et al., 2020; Fedewa SA, Kazerooni EA, Studts JL, et al. State Variation in Low-dose CT Scanning for Lung Cancer Screening in the United States. J Natl Cancer Inst, 2020; Kim et al., 2008; Schnoll et al., 2003; Hahn et al., 2006). Overall adherence to annual CT screening has been reported to be between 37 and 65% in CT screening programmes (Cattaneo et al., 2018; Hirsch et al., 2019; Tanner et al., 2020; Lopez-Olivo et al., 2020). This is comparable to screening for breast and colon cancer (Breen et al., 2007; Swan et al., 2000). This contrasts with the adherence rates reported in the trial setting of NLST where over 95% of screening participants complied with the screening protocol (Aberle et al., 2011).

Over the last 5 years there has been a growing interest in multivariate risk models of lung cancer risk (Spitz et al., 2007; Cassidy et al., 2008; Tammemägi et al., 2013; Tammemagi et al., 2011; Kovalchik et al., 2013). The main risk variables of age and smoking history have to date provided the basis of eligibility criteria for lung cancer screening trials, including the lung cancer RCTs (Aberle et al., 2011; de Koning et al., 2020; Pastorino et al., 2019). However, recent studies show that age and pack year criteria alone are not good predictors of lung cancer risk (Bach and Gould, 2012; Young and Hopkins, 2013), and that by adding other risk variables, the predictive utility of these risk models is substantially improved (Spitz et al., 2007; Cassidy et al., 2008; Tammemägi et al., 2013; Tammemagi et al., 2011; Kovalchik et al., 2013). The additional risk variables include family history of lung cancer, self-reported chronic obstructive pulmonary disease (COPD), asbestos or dust exposure, and body mass index (BMI). To our knowledge, no one has examined the effect of individualising a person's lung cancer risk on their adherence to CT screening. The primary aim of this small community-based pilot study of CT screening was to examine the utility of offering a personalised gene-based risk test (acceptability) and its effect on attendance to baseline screening (uptake) and subsequent positive CT scans (adherence).

2. Methods

2.1. Screening participants

A prospective single arm cohort study was initiated from the Genomics Institute and Oncology Department of the El Camino Hospital (Mountain View, California) in November 2010 (Lam et al., 2015). Screening volunteers were volunteers who responded to local advertisements or referral from their primary care physician. Volunteers who met the following criteria, aged at least 50 years old with a history of cigarette smoking of at least 20 pack-years, were offered a one-off (baseline) low-dose CT scan by our study co-ordinator at the El Camino Hospital (Lam et al., 2015). At recruitment (visit 1), screening participants were also offered an optional lung cancer risk assessment that involved a short clinical history questionnaire and non-invasive cheek swab. The swab provided a DNA sample for subsequent genotype analysis, underpinning a previously published and validated gene-based lung cancer risk algorithm (Respiragene™, www.synergenz.com) (Young et al., 2009a, 2009b, 2011c, 2010d, 2014e). Following visit 1, subjects underwent a baseline CT scan (visit 2, see below) and returned for the results of their personalised gene-based risk score and baseline scan result (visit 3).

2.2. Gene-based lung cancer risk score

The clinical genotype testing was performed by a CLIA-approved laboratory, operated by PHD Diagnostics LLC, based in Covington, Kentucky. Cheek swab samples from each screening participant were couriered at room temperature to the lab where they were processed using a salt-based DNA extraction method to yield genomic DNA. Genotyping for a panel of 20 published single nucleotide polymorphisms (SNPs), previously associated with COPD and/or lung cancer (Young et al., 2009a, 2009b, 2010c), was done using a Taqman-based polymerase chain reaction method (Young et al., 2011). The composite lung cancer risk score was calculated using a published algorithm based on the clinical risk variables (age, self-reported COPD and family history of lung cancer (Young et al., 2009a, 2009b, 2011c, 2010d, 2014e) together with the genotype data for 20 validated risk SNPs (Young et al., 2009a, 2009b, 2010c). Composite risk was sub-grouped into Moderate ($\leq$3), High (4–5) and Very High ($\geq$6) risk score categories. On visit 3, the composite gene-based risk score results were given to screening participants at the same time as their baseline CT screening result. Three study participants failed to attend for their baseline CT although lung cancer risk testing was done. This study was approved by the Institutional Review Board at El Camino Hospital (ECH-09–29) (Lam et al., 2015).

2.3. CT screening and Follow-up

Baseline CT scans (visit 2) were done using multi-detector computed tomography scanners with a minimum of four channels. Acquisition parameters were selected with the goal of reducing exposure to an average effective dose of 1.5 mSv. CT scans were read by a specialist radiologist. Repeat scanning and diagnostic follow-up was limited to those with a positive baseline CT scan using NLST criteria of $\geq$ 4 mm (Aberle et al., 2011), with scheduling according to IELCAP recommendations (Lam et al., 2015). After baseline risk and CT assessment, current smokers were offered participation in the El Camino Hospital's smoking cessation programme. Participants were followed for screening-related outcome events that occurred through to February 1, 2014. "Overall" adherence to CT was defined as "Timely and Late" adherence to scheduled CT screening following a positive scan. "Timely" adherence was defined as scheduled attendance within 4 weeks (Lam et al., 2015). "Late" adherence was assigned to those who attended more than four weeks after their scheduled attendance (Lam et al., 2015).

2.4. Statistical analysis

Basic demographics were compared with those from the NLST trial for comparative purposes. Of the 157 screening volunteers who accepted and underwent baseline risk assessment at visit 1, 154 subjects (98%) returned on visit 3 to receive their gene-based risk score result and baseline CT screening results. Analyses of baseline characteristics

(including risk) is based on 157 participants, while CT-related outcomes including adherence was based on the 154 that completed the full baseline screen (including both CT and lung cancer risk score). Outcomes according to lung cancer risk score was compared using Fishers Exact test with statistical significance when the P value (2-tailed) reached $P < 0.05$.

3. Results

3.1. Screening participant demographics

One-hundred and fifty seven participants volunteered and underwent baseline assessment including a gene-based lung cancer risk assessment; mean age at entry was 64 years (range 50–95 yrs), 59% of the participants were women, 94% were Caucasian and 71% were ex-smokers (Table 1). Forty-three percent of study participants were eligible for CT screening according to NLST-based age and pack year criteria, 15% reported a past diagnosis of COPD and 29% had a positive family history (first degree relative) of lung cancer (2 fold greater than in the average smoker in this age band) (Young et al., 2009a, 2009b, 2011c). Following the calculation of each subject's composite risk score, 27% (N = 43) were assigned as moderate risk category, 27% (n = 42) were high risk and 46% (N = 72) were very high risk for lung cancer based on their personalised multivariate gene-based risk score algorithm (Table 1) (Young et al., 2009a, 2009b).

Table 1
Demographics of the screening participants compared to the NLST participants in the CT arm.

Demographic variable	Current study (N = 157)	NLST - CT arm (N = 26,722)
Gender		
Male	64 (41%)	15,777 (59%)
Female	93 (59%)	10,952 (41%)
Mean age (SD) yrs	64.4 (±8)	61.4 (±5)
Age Distribution yrs		
- 50–55	15 (10%)	2 (<0.1%)
- 55–59	34 (22%)	11,440 (43%)
- 60–64	38 (24%)	8,170 (31%)
- 65–69	29 (29%)	4,756 (18%)
- 70–74	24 (15%)	2,353 (9%)
- 75+	16 (10%)	1 (<0.1%)
Race		
Caucasian	148 (94%)	24,289 (91%)
African American	1 (1%)	1,195 (5%)
Hispanic	5 (3%)	479 (2%)
Asian	2 (1%)	559 (2%)
Native American	1 (1%)	92 (<0.1%)
Smoking status		
- Current	46 (29%)	12,862 (48%)
- Former	111 (71%)	13,860 (52%)
Mean Pk Yrs	46 (±25)	56 (±24)
Family history of lung cancer (1st degree relative)	46 −29%	5,815 −22%
Self-reported COPD	23 −15%	4,674 −18%
NLST Criteria		
- - Age (55–74 yr)	125 (80%)	NR
- - Pk Yrs 30+	122 (78%)	NR
- - Quit ≤ 15 yrs	92 (59%)	NR
- - All three above	68 (43%)‡	>99%
Lung Cancer Risk Score		
- Moderate	43 (27%)	ND
- High	42 (27%)	ND
- Very High	72 (46%)	ND

NR-Not Reported, ND-Not Done.‡ 53% met criteria for the US Preventative Services Task Force (2013 eligibility criteria) and over 90% meet the 2021 criteria.

3.2. Baseline composite lung cancer risk score

Of the 157 screening participants who were recruited, 157 (100%) agreed to undertake gene-based risk assessment. Of these, 32 (20%) were assigned their risk of lung cancer solely on SNP genotype data (Fig. 1a), while a further 68% (50 + 16 + 40 = 106/157) were assigned risk by combining SNP data with age and/or the clinical variables of family history or COPD. In other words, for 88% of participants lung cancer risk was based in whole or part on their SNP genotype results (Fig. 1a). Only 12% (N = 19/157) of people were assigned their risk based on age and clinical variables with no SNP (genetic) contribution (Fig. 1a). Age was the second most prevalent variable scoring in the risk algorithm, contributing to risk scores in 68% (N = 107/157) of participants (Fig. 1b), with COPD and family history each scoring in 15% (N = 23/157) and 29% N = 46/157) of study participants respectively (Fig. 1c). This confirms that SNP data may make a considerable and unique contribution to lung cancer risk assignment above that of the traditional clinical variables such as family history (88% vs 29% respectively) (Tammemägi et al., 2013; Tammemagi et al., 2011a, 2011b; Claassen et al., 2010).

The addition of the SNP genotypes to the clinical risk algorithm (based on age and other clinical variables) has been previously shown to modestly increase the predictive utility (AUC) of a risk algorithm using clinical variables alone (Young et al., 2009a, 2009b, 2011c, 2010d, 2014e). In the current study, adding SNP genotype data to the clinical risk score moved 28% of the current/former smokers (44/157) into different risk categories with 22% moving to a higher risk category and 6% to a lower risk category. This means reassignment of risk classification affected 28% of participants with addition of the SNP genotype data to the clinical risk score (Fig. 2). The addition of family history of lung cancer or self-reported COPD to re-assigning the clinical risk category was seen in 17% and 11% of screening participants respectively (data not shown). We conclude that age and the composite SNP genotypes (genetic risk score) made the greatest contribution to assignment of the lung cancer risk category.

3.3. CT screening outcomes

Of the 157 screening participants enrolled in visit 1, 154 (98%) returned for visit 2 and underwent a baseline CT scan with subsequent follow-up for positive scans as needed (N = 107). This comprised 55 abnormal scans on initial (baseline) screening and 52 on follow-up scans. The rate of positive baseline CT screening tests was 35.7%, higher than the 27% reported in the NLST (Aberle et al., 2011; Lam et al., 2015). One positive screen (3.7%) required invasive diagnostic follow-up, which was uncomplicated. No interval lung cancer was detected. One incident case of small cell lung cancer, diagnosed after his initial screening visit, resulted in death. The rate of "timely" adherence (within 4 weeks of scheduled follow-up) to diagnostic follow-up in scan positive subjects was only 43% (46/107 positive scans) while "Overall" adherence to positive scans, including those with "timely" and "late" follow-up, was 63% (Table 2) consistent with the literature (Lam et al., 2015).

Importantly, "Overall" adherence to CT screening was greatest in those with very high risk (71%), compared to high risk (52%) or moderate risk (52%), with greater adherence in the very high risk compared to other risk categories (OR = 2.3, $P < 0.05$). "Timely" adherence to CT screening was also greater in those with very high risk (51%), compared to high risk (30%) or moderate risk (38%) (trend only, OR = 2.1, two-tailed P = 0.08).

3.4. Smoking outcomes

Of the 157 participants, 46 (29%) were current smokers and were offered smoking cessation counseling after baseline assessment. Of these 46 people, 23 (50%) accepted counseling but did not undergo routine

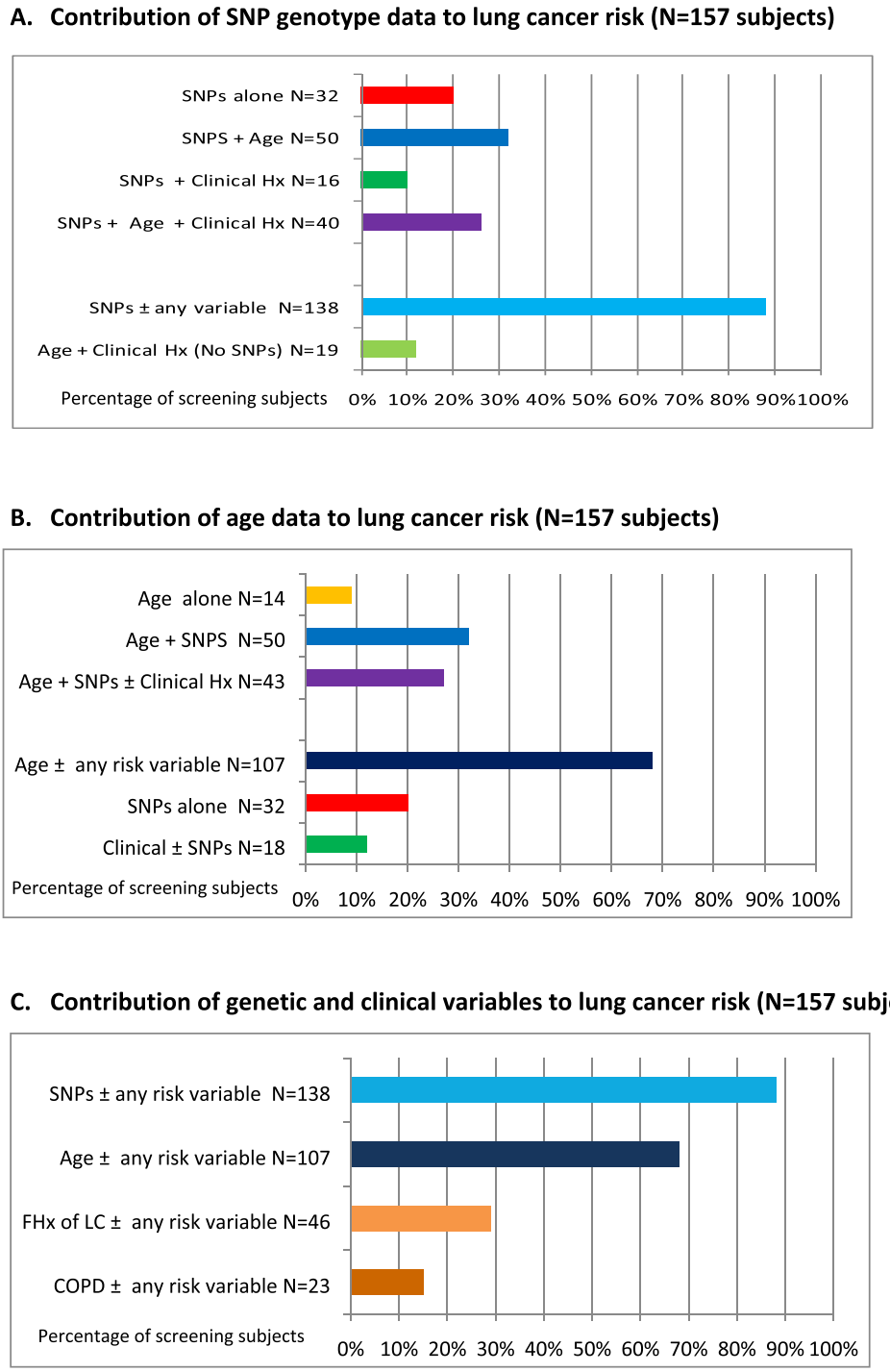

Fig. 1. Percentage of study participants (N = 157) whose lung cancer risk score was contributed by the SNP genotype, age and clinical risk variables (Lam et al., 2015). Contribution of SNP genotype data to lung cancer risk (N = 157 subjects) Contribution of age data to lung cancer risk (N = 157 subjects) Contribution of genetic and clinical variables to lung cancer risk (N = 157 subjects).

post-counseling follow up. The lung cancer risk categories for this group were moderate in 7 (30%), high in 7 (30%) and very high in 9 (39%). Although the sample size is small, these frequencies are comparable to the distribution of scores overall suggesting no significant demotivating effect on quitting smoking from risk testing.

4. Discussion

To our knowledge, this is the first study reporting results of low-dose CT lung cancer screening in a community hospital setting where risk assignment using a multivariate gene-based risk algorithm was offered. Compared to the NLST results, those from this study showed a higher rate of positive initial screening tests (36% vs 27%) and significantly decreased adherence (63% vs 95%) highlighting the difficulties of generalising the NLST mortality benefits in the broad deployment of CT screening outside highly specialised research-focused institutions. The offer of a gene-based risk test was well accepted (100% acceptance) and associated with a 98% uptake rate for screening. Those in the highest risk category based on their personalised risk score was associated with greater adherence to CT follow-up compared to those at lesser risk (71%

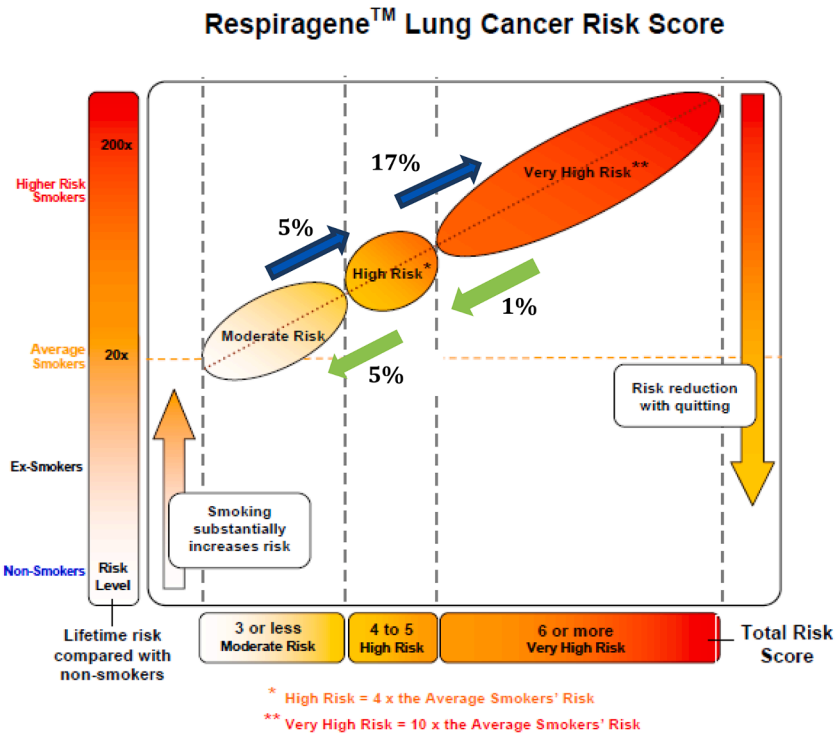

Fig. 2. Percentage of screening participants for whom re-assignment of Respiragene risk score category occurred when their individualised SNP genotype data (genetic risk score) were added to the clinical data to derive the overall risk category (Young et al., 2011, 2010). A total of 28% of participants moved to a different risk category when SNP genotype data was combined with clinical risk scores (22% moved rightward to a higher risk category while 6% moved leftward to a lower risk category).

Table 2
Adherence to CT screening follow up according to the Lung Cancer Risk Category in study participants (Moderate, High and Very High).

Adherence	Lung cancer risk score category			
	Moderate	High	Very High	Total
Timely Adherence N = 46 (%)	8/21 (38%)	8/27 (30%)	30/59[2] (51%)	46/107 (43%)
Overall Adherence N = 67 (%)	11/21 (52%)	14/27 (52%)	42/59[1] (71%)	67/107 (63%)
No Adherence N = 40 (%)	10/21 (48%)	13/27 (48%)	17/59 (29%)	40/107 (37%)
Positive CT Scan/ Total Screened N = 154 (%)	21/43 (49%)	27/41 (66%)	59/70 (84%)	107/154 (69%)
All Study Participants N = 157 (%)	43 (27%)	42 (27%)	72 (46%)	157 (100%)

Overall Adherence (Timely and Late adherence) in "Very High" risk compared to "High" and "Moderate" risk groups: Odds Ratio = 2.3 95% CI = 1.02–5.05, P = 0.047).
Timely Adherence compared to Late and No Adherence in "Very High" risk compared to "High" and "Moderate" risk groups: Odds Ratio = 2.1 95% CI = 0.94–4.55, P = 0.08 and P = 0.04 on 1-tailed).

in the very high risk group vs 52% in the other 2 lower risk categories). The results of this pilot study suggest that the inclusion of a gene-based risk tool in a CT screening programme of current or former smokers may help engage high risk smokers in screening and potentially improve adherence to screening.

The wide variation in risk among those eligible for NLST-based CT screening has been shown to vary by as much as 10–50 fold (Kovalchik et al., 2013; Bach and Gould, 2012). Multivariate risk models, that include risk variables in addition to age and pack years, have shown significant improvement in risk prediction, best observed by increasing AUC analyses (Spitz et al., 2007; Cassidy et al., 2008; Tammemägi et al., 2013; Tammemagi et al., 2011; Kovalchik et al., 2013). Biomarkers of risk have been found to improve risk models when added to clinical variables. Genetic markers based on SNP genotypes have been shown to improve clinical risk models for lung cancer as reported by both Spitz and Young (Spitz et al., 2009; Young et al., 2009, 2011, 2010). In the current study, a SNP-genotype based risk algorithm, which included recognised clinical variables of lung cancer risk, was used to assign risk level to screening participants. This is analogous to using family history or clinical variables (eg. Gail Score), with gene testing (eg. BRCA), to personalise screening for breast or prostate cancer according to individualised risk (Chowdhury et al., 2013). In the current study, where a 20 SNP genotype panel was used to help refine risk assignment, we found that for 20% of participants SNP-genotype was the sole contributor to assigning risk for lung cancer. We also found that the SNP genotype contributed to the risk score in another 68% of participants (88% overall), and was the most influential variable in assigning risk, relative to the clinical variables. Most importantly, adding SNP-genotype data to an individual's risk score resulted in re-assignment of risk category in 28% of participants. This result is very similar to the results we obtained in a sub-study of the NLST where a 10 SNP panel reassigned risk in 26–31% of participants in the NLST using net reclassification improvement index (NRI) analyses (Young et al., 2014). We conclude from these results that SNP data provides a useful addition to clinical variables in assigning risk and that this may have utility in engaging smokers in CT screening (Patel et al., 2012; Senft et al., 2019; Young and Hopkins, 2013). In the current study, 98% (154/157 high risk smokers) of those deemed eligible for screening actually attended to undergo CT screening. This was in conjunction with receiving their genetic test result. This finding supports a recent telephone survey suggesting gene-based risk testing enhances interest in CT screening in those testing at greatest risk (Patel et al., 2012; Young and Hopkins, 2012). A similar approach has recently been proposed for screening in breast and prostate cancers (Chowdhury et al., 2013).

Behavioural studies consistently show that those who perceive themselves to be at greatest risk, are more interested in screening and are more likely to participate in screening. This has also been shown to be the case when screening for lung cancer (Patel et al., 2012; Young and Hopkins, 2012; Griffiths et al., 2012; Silvestri et al., 2007; Kim et al., 2008; Schnoll et al., 2003; Hahn et al., 2006). Data from the NLST shows

that 33% of participants in the NLST have underlying COPD and 26% have a positive family history of lung cancer (Young et al., 2013). These frequencies are greater than would be expected in the general smoking population (Young et al., 2009; Tammemagi et al., 2011) and suggest a "volunteer bias" toward higher risk smokers attending for screening (Young and Hopkins, 2014). With regards to a family history of lung cancer, it is notable that the frequencies of 29% in the current trial mirrors the 26% observed in the NLST, between 2 and 3 fold greater that seen in adult smokers in general (9%) (Young et al., 2009). Despite this, the range of risk across people eligible on age and smoking criteria alone is huge (Kovalchik et al., 2013; Bach and Gould, 2012), thereby undermining the risk-to-benefit ratio of screening. This wide variation of risk in those eligible for screening is one of the single most important concerns surrounding screening (Bach and Gould, 2012). In a large telephone survey, investigating smokers' decision making according to different risk scenarios, increased genetic risk of lung cancer was associated with greater interest in CT screening (Young and Hopkins, 2012). This observation has been corroborated in a screening study at Vanderbilt University where 83% of participants reported they were "more likely to get lung cancer screening" if they underwent gene-based risk test for lung cancer (Senft et al., 2019). These findings suggest a possible role for gene-based risk testing in improving the currently low uptake of lung cancer screening in eligible at risk cohorts.

Another important aspect of efficacious CT screening is the adherence to CT screening protocols, particularly to timely follow-up of positive scans (Montes et al., 2007; Cattaneo et al., 2018; Hirsch et al., 2019; Tanner et al., 2020; Lopez-Olivo et al., 2020). Overall adherence to annual CT screening has been reported to be between 37 and 65% (Montes et al., 2007; Cattaneo et al., 2018; Hirsch et al., 2019; Tanner et al., 2020; Lopez-Olivo et al., 2020; Patel et al., 2012; Young and Hopkins, 2012a, 2013b, 2013c, 2014d; Griffiths et al., 2012; Silvestri et al., 2007; Kim et al., 2008; Schnoll et al., 2003; Hahn et al., 2006; McCaul et al., 1996; Bloss et al., 2011; Weinstein et al., 2005; Nichols et al., 2017; Senft et al., 2019; Spiro, 2007; Park et al., 2013; Breen et al., 2007; Swan et al., 2000; Spitz et al., 2007, 2009; Cassidy et al., 2008; Tammemägi et al., 2013; Tammemagi et al., 2011a, 2011b; Kovalchik et al., 2013; Bach and Gould, 2012; Lam et al., 2015; Young et al., 2009h, 2009i, 2011j, 2010k, 2014l, 2013m, 2010n; International Early Lung Cancer Action Programme, 2006; Claassen et al., 2010; Chowdhury et al., 2013; West and Sohal, 2006; Hopkins et al., 2011, 2012) and contrasts with the adherence rates reported in the trial setting of NLST where over 95% of screening participants complied with the screening protocol (Aberle et al., 2011). This level of adherence may not be achievable in screening centers outside the setting of a clinical trial where participants are highly motivated and the programme resourced to achieve high levels of adherence. These studies suggest that both uptake and adherence to CT screening for lung cancer may be, in part, related to a smoker's perception of self-risk and their doctor's perception of benefit over harm.

Given that in community based studies, adherence to screening in general varies between 40 and 60%, we were interested to find that our study (Lam et al., 2015), the "Overall" adherence was 71% in those at Very High risk, statistically greater than in those at Moderate and High risk (52%) (OR = 2.3, P = 0.05) (Lam et al., 2015). Moreover, in the screening participants assigned as Very High risk, the adherence to timely screening was nearly two-fold greater than those in the lower risk categories (OR = 2.1, P = 0.08, Table 2). We found no evidence of a demotivating effect in those at Moderate risk (52% adherence) given they had a similar adherence to those at high risk (52% adherence). This suggests that risk stratification helps motivate screening participants, by increasing motivational tension, improving adherence to screening based on a greater sense of fear. This not only reinforces the public health message, that smoking puts all smokers at increased risk of lung cancer, but refines it for individuals by personalising their risk relative to the average smoker (Fig. 2). In a related context there is preliminary data suggesting that smokers undergoing this gene-based risk testing are more likely to use nicotine replacement products and more likely to quit smoking (West and Sohal, 2006; Hopkins et al., 2011, 2012). While the current trial was not designed to study this outcome, and no long term follow-up data on quit rates was recorded, we found no demotivating effects from gene testing. Further studies will be needed to confirm this finding and results are pending (Senft et al., 2019).

There are many limitations to this study. First, it is small and may not fully reflect the wider experience with community based CT screening for lung cancer. Second, as screening participants were almost exclusively white, engagement of other ethnic groups in CT screening remains unknown. Third, the current study was a single arm pilot study with no control group, designed before the results of the NLST were known. This, together with specific cohort effects like older age distribution (Table 1), might explain in part the higher scan positive rate of 36% in the current study compared to NLST. Fourth, there was no assessment of the primary care doctors' opinion of risk testing nor was there a control arm where genetic risk testing was not done, so the effects of gene-based risk testing on uptake and adherence to screening requires replication. It is possible, that clinically-based multivariate risk testing (without genetic data) may also improve adherence to screening although this has not been assessed to date. However, the results of this study support other studies showing that SNP data does add useful predictive utility to risk assignment for lung cancer (Young et al., 2014; Spitz et al., 2009; Chowdhury et al., 2013; Young and Hopkins, 2013) and that this may help improve engagement of smokers, and possibly their primary care physicians, in the process of screening.

In conclusion, although CT screening is widely recommended, increasing uptake and maximising the benefits while reducing the harms must remain an important goal in the successful implementation of lung cancer screening. Studies on the clinical utility of using multivariate risk models to optimise screening participation, increase lung cancer detection rates, and increase the number of lives saved with screening, must remain a priority.

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Author contribution

RPY contributed to the study conception and design and methodology as well as funding acquisition; data acquisition, analysis and interpretation of the results; drafting and review for important intellectual content and final approval of the manuscript. VKL contributed to the data acquisition, formal analysis and final approval of the manuscript. RJS contributed to the study design, project management, analysis and interpretation of the results, drafting and review of the manuscript and final approval of the manuscript. PB contributed to the funding acquisition; study conception. EC contributed to data acquisition, analysis and interpretation of the results; review for important intellectual content.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: RPY is an unpaid scientific advisor, founder and shareholder of the company Synergenz Bioscience who hold patents related to gene-based risk testing of lung cancer. PB is an advisor and shareholder of the company Synergenz Bioscience who hold patents related to gene-based risk testing of lung cancer. The remaining authors have no significant conflicts of interest with respect to the subject matter discussed in this correspondence.

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