between a change in sweat chloride and improvement in FEV₁ in individual patients with cystic fibrosis (CF) who received ivacaftor in phase 3 clinical trials.¹ They suggest that this lack of correlation between changes in sweat chloride in the ivacaftor trials should not diminish the potential usefulness of sweat chloride for predicting clinical outcomes.

Regarding the usefulness of using change in sweat chloride as an end point, it should be pointed out that it was and continues to be used effectively by companies developing therapies that target the CF transmembrane conductance regulator gene or protein. For example, for the ivacaftor program, it was used to establish proof of principle of drug activity, as a pharmacodynamic biomarker to select and enrich CF patient study populations that may best respond to the drug, and, in association with change in FEV₁, as a factor in dose selection.

The implicit issue in the correspondence appears to be the extent to which change in sweat chloride could be used as a primary end point to establish efficacy for regulatory purposes (ie, approval of a drug for marketing). Such qualification of a pharmacodynamic biomarker as a surrogate end point is a high bar to achieve, as robust scientific evidence would be needed that demonstrates that changes in sweat chloride beyond a specific level in a specific CF population would predict clinical benefit to the same extent that a clinical end point (an improvement in how a patient feels, functions, or survives) would.² Because of such a high level of evidence required, most pharmacodynamic biomarkers are used, as has been the case to date for the ivacaftor program, to guide drug development, whereas clinical end points (or in the case for ivacaftor, the surrogate end point, FEV₁) provide the basis for regulatory approval. With the arrival and continued development of a new class of classes of CF therapies that have the potential to address the central defect that results in CF, we, like the CF community, are happy that we have reached such a time that we can have a discussion on the use of change in sweat chloride or other possibly more accurate pharmacodynamic biomarkers that may reflect CF transmembrane conductance regulator function³ as end points in clinical trials.

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REFERENCES

Targeted CT Image Screening and Its Effect on Lung Cancer Detection Rate

To the Editor:

Although we broadly endorse the American College of Chest Physicians lung cancer screening guidelines, outlined in the recent article by Detterbeck et al in CHEST (May 2013), we disagree that the impact of differing eligibility criteria are unknown.²³

The assumption underlying the National Lung Screening Trial (NLST) eligibility criteria is that they identify those at greatest risk and the most to gain from screening. The former assumption can be easily tested by comparing the number of lung cancers detected per year per person screened (lung cancer detection rate [LCDR]) across lung cancer screening studies with differing eligibility criteria.² Although this metric does not assess lives saved, it does reflect the precision of risk prediction.²³ Our analysis suggests that there is surprising consistency in the LHDR across screening studies using CT imaging, despite differing age and smoking criteria (Table 1). Primarily, the higher age and smoking history criteria of the NLST did not translate into significantly more cancers detected (reflected in the LHDR) than other screening programs that screened people with wider age and pack-year histories. LHDR is an important metric as its inverse estimates the number needed to screen in a year to detect one lung cancer (NND), which is about 110 to 120 people in the case of NLST. This has important implications with respect to optimizing the cost-to-benefit and benefit-to-harm ratios, which remain major concerns impeding the wider adoption of lung cancer screening.²³

Recently, we showed that when genetic and COPD-based risk variables are combined with age and smoking histories (eg, multivariate risk model),² LHDR can be doubled (Table 1).² This translates to a halving of the number of people needed to screen to detect one lung cancer and a reduction in costs associated with lung cancer detection. The NLST-validated Prostate, Lung, Colorectal, and Ovarian-based model includes variables that encompass genetic risk (family history of lung cancer) and the presence or risk of COPD (self-reported COPD and low BMI). By improving the efficiency of screening (lowering the NND), through multivariate models with greater predictive utility than NLST-based risk prediction, we anticipate the absolute number of false-positives detected and investigated (benign and indolent “overdiagnosed” nodules) will be reduced.²³

We conclude that while the NLST successfully showed that CT image screening reduces lung cancer deaths, further refinement of lung cancer screening eligibility criteria might better target the highest-risk smokers. This could significantly improve the LHDR and lower the costs to detect lung cancer. Further analysis will be needed to determine the benefit with respect to lives saved.
Table 1—LCDR in the CT Imaging Arms of Recent Lung Cancer Screening Studies Compared With the NLST

<table>
<thead>
<tr>
<th>Study (Eligibility Criteria)</th>
<th>Subgroup Analysis</th>
<th>N</th>
<th>Duration</th>
<th>Lung Cancer Cases</th>
<th>LCDR/y</th>
<th>NND/y</th>
</tr>
</thead>
<tbody>
<tr>
<td>NLST (55-74 y, ≥ 30 pk y, &lt; 15 y quit)</td>
<td>CT imaging arm</td>
<td>26,722</td>
<td>3 y*</td>
<td>720</td>
<td>0.90</td>
<td>111</td>
</tr>
<tr>
<td>DLST (50-70 y, ≥ 20 pk y, &lt; 10 y quit)</td>
<td>CT imaging arm</td>
<td>2,052</td>
<td>4 y</td>
<td>69</td>
<td>0.84</td>
<td>119</td>
</tr>
<tr>
<td>NELSON (50-75 y, ≥ 15 pk y, &lt; 10 y quit)</td>
<td>CT imaging arm</td>
<td>7,582</td>
<td>3 y</td>
<td>200</td>
<td>0.88</td>
<td>114</td>
</tr>
<tr>
<td>COSMOS (≥ 50 y, ≥ 20 pk y, &lt; 10 y quit)</td>
<td>CT imaging single arm</td>
<td>5,203</td>
<td>4 y</td>
<td>175</td>
<td>0.84</td>
<td>119</td>
</tr>
<tr>
<td>PLuSS (50-79 y, ≥ 12.5 pk y, &lt; 10 y quit)</td>
<td>CT imaging single arm, total Normal lungs b</td>
<td>3,642</td>
<td>3 y</td>
<td>99</td>
<td>0.91</td>
<td>110</td>
</tr>
<tr>
<td></td>
<td>COPD (GOLD I-IV)</td>
<td>1,495</td>
<td>15</td>
<td>30</td>
<td>0.33</td>
<td>303</td>
</tr>
<tr>
<td></td>
<td>CTE</td>
<td>1,486</td>
<td>67</td>
<td>1.50</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1,471</td>
<td>75</td>
<td>1.70</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>NLST (55-74 y, ≥ 30 pk y, &lt; 15 y quit)</td>
<td>PLCO model c — CT imaging arm(BMI, Hx COPD, FHx LC)</td>
<td>13,014</td>
<td>6.5 y</td>
<td>954</td>
<td>1.22</td>
<td>82</td>
</tr>
<tr>
<td>De Torres et al. (≥ 40 y, smokers)</td>
<td>COPD = CT arm(GOLD I-II)</td>
<td>333</td>
<td>2.6 y</td>
<td>20</td>
<td>2.31</td>
<td>43</td>
</tr>
</tbody>
</table>

Lung cancer detection rate (lung cancers detected per year per person screened) in the CT imaging arms of recent lung cancer screening studies compared with the NLST. COSMOS = Continuous Observation of Smoking Subjects; CTE = CT imaging-emphysema; DLST = Danish Lung Cancer Screening Trial; FHx = family history of lung cancer; GOLD = Global Initiative for Chronic Obstructive Lung Disease; Hx COPD = self-reported COPD; LCDR = lung cancer detection rate; NELSON = The Dutch-Belgian Randomized Lung Cancer Screening Trial; NLST = National Lung Screening Trial; NND = the number of people needed to be screened for 1 y to detect one lung cancer; PLCO = Prostate, Lung, Colorectal, and Ovarian; PLuSS = The Pittsburgh Lung Screening Study.

*Data for the NLST were for the first 3 y when yearly CT image screening was performed.

b Normal lungs means no airflow limitation on spirometry and no emphysema on CT imaging.

c The model derived from the Prostate Lung, Colorectal and Ovarian study.

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Response

To the Editor:

We agree with the fundamental message in the letter by Dr Young and Ms Hopkins in response to the American College of Chest Physicians lung cancer guidelines chapter on screening in CHEST. Their message is that screening only people at higher risk will provide more “bang for the buck,” that is, result in detection of more lung cancers per person screened. The open questions are (1) what does this mean in terms of reducing the number of deaths from lung cancer in the screened population, and (2) how should the greater detection per person screened be balanced with the fact that this results in a smaller number of people considered eligible for screening?

The table provided by the authors is interesting. A slightly different calculation of the number of cancers detected over the course of each screening study demonstrated greater differences (see Table 5 in Bach et al.). These differences were not explained by a comparison of the stringency of the entry criteria for the studies. We should remember that the entry criteria may not reflect the overall average risk of those patients actually enrolled.

Several different risk prediction models have been developed, and some have been validated in independent datasets. However, a comparison of the risk prediction of the different models reveals some generally similar trends, but also significant differences between them when applied to individual actual people (Lynn Tanone, MD, and Frank Detterbeck, MD, unpublished data, 2013). This underscores the complexity and the difficulty in relying on only one method.

References


