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# BMJ Open

## Similarity of Chest X-ray and Thermal Imaging of Focal Pneumonia (short title: Thermal Imaging of Pneumonia)

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1 Similarity of Chest X-ray and Thermal Imaging of Focal Pneumonia

2 (short title: Thermal Imaging of Pneumonia)

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24 38 ABSTRACT  
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28 40 Objective: To determine the similarity of thermal imaging (TI) to chest x-ray (CXR)  
29 41 in the setting of focal consolidative pneumonia.  
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34 43 Setting: A large, 973 bed teaching hospital in Boston, Massachusetts  
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38 45 Participants: 47 patients enrolled, 15 in a training set, 32 in a test set. Age range  
39 46 10 months - 82 years (media = 50 years)  
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44 48 Materials and Methods: Subjects received CXR with subsequent TI within 4 hours of  
45 49 each other. CXR and TI were assessed in blinded random order. Presence of focal  
46 50 opacity (pneumonia) on CXR (the outcome parameter) was recorded. For TI,  
47 51 presence of area(s) of increased heat (pneumonia) was recorded. Fisher's exact test  
48 52 was used to assess the significance of the correlations of positive findings in the  
49 53 same anatomic region.  
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3 55 Results: With TI compared to the CXR (the outcome parameter), sensitivity was  
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5 56 80.0% (Confidence intervals: [29.9%, 98.9%], specificity was 57.7% (Confidence  
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7 57 intervals: [37.2%, 76.0%]). Positive predictive value of TI was 26.7% (Confidence  
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9 58 intervals: [8.9%, 55.2%]) and its negative predictive value was 93.8% (Confidence  
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11 59 intervals: [67.7%, 99.7%]).  
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14 60  
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16 61 Conclusions: This feasibility study confirms proof of concept that chest TI is  
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18 62 consistent with CXR in suggesting similarly localized focal pneumonia with high  
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20 63 sensitivity and negative predictive value. Further investigation of TI as a point of  
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22 64 care imaging modality is warranted.  
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24 65  
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26 66 Strengths and Limitations:  
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30 68 Strengths:

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33 69 • Proof of concept suggesting that Thermal Imaging (TI) is a valid,  
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35 70 innovative, and inexpensive technology useful for diagnosing bacterial  
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37 71 pneumonia  
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39 72 • Proof of concept suggesting that Thermal Imaging (TI) is a rapid  
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41 73 means of diagnosing focal pneumonia in high throughput settings  
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44 74 • Proof of concept suggesting that Thermal Imaging (TI) is a valid and  
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46 75 innovative technology useful in diagnosing pneumonia in resource  
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48 76 limited regions of the world  
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54 78 Limitations:  
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4 79 • As this is a proof of concept study, it does not have adequate power to  
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6 80 be definitive and cannot replace chest xray for detecting focal  
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8 81 pneumonia  
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10 82 • As this is a proof of concept study, limitations of the technology have  
11  
12 83 not been fully discerned, and at present include adipose tissue and  
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14 84 interpretation, but may include other concerns which will require  
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16 85 higher numbers of patients enrolled.  
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20 86 Word Count: 2590  
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- 22  
23 87• Data Sharing: There is no additional unpublished data from the study. Data is  
24  
25 88 available to any researcher who is interested in the data, and will be able to be  
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27 89 accessed through Dyad and/or through correspondence with the contributing  
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29 90 authors.  
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### 33 93 Introduction 34 35 94

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37 95 This study investigates the degree to which thermal imaging (TI) and chest x-ray  
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39 96 (CXR) agree in detecting similarly localized focal pneumonia. Often a clinically  
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41 97 challenging diagnosis, bacterial pneumonia remains a major cause of morbidity and  
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43 98 mortality worldwide, particularly in under-resourced environments (1-3). Expert  
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45 99 panels, including the World Health Organization (WHO), have formulated algorithms  
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47 100 to enhance clinical accuracy (4), typically focusing on aspects of the medical history  
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49 101 and physical examination to determine the likelihood of bacterial pneumonia. Despite  
50  
51 102 having these algorithms, CXR is generally performed to confirm the diagnosis in  
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53 103 severe infections (5-16). If TI results are similar to CXR, it might substitute for CXR  
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55 104 when CXR is not available. In resource-limited environments, where 2/3 of the  
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3 105 world's population has no access to diagnostic imaging (17-18), the potential use of  
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5 106 TI in point of care screening could aid decision making to treat for pneumonia.  
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7 107 Point of care imaging utilizing ultrasonography to diagnose pneumonia is attracting  
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9 108 interest (19-20). However, ultrasonography requires costly equipment and specific  
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11 109 expertise for image acquisition and interpretation.  
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16 111 Anecdotal reports suggest that TI has potential for detecting pneumonia (21-22).  
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18 112 These case reports and methodologies have not been subjected to systematic  
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20 113 blinded assessment. In this initial proof of concept investigation, we compared TI to  
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22 114 CXR in patients suspected of having acute pneumonia.  
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26 116 With recent advances in infrared technology and increasing use assessing home heat  
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28 117 loss, low-cost thermal cameras have become available, currently costing as little as  
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30 118 \$200-\$300 (Flir.com). Installation of shielded radiographic rooms can cost hundreds  
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32 119 of thousands of dollars. Portable x-ray units capable of performing CXR can cost as  
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34 120 little as \$600-\$800 (dotmed.com). If uninsured, patient cost of a CXR in the US is  
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36 121 \$200-\$400 or, if insured, a co-pay of \$10-\$50 (23).  
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41 123 For TI there are no additional costs beyond cost of the camera. TI cameras are  
42  
43 124 portable and operate with rechargeable batteries. TI is essentially identical to taking  
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45 125 a "snap and shoot" photograph and can be done in seconds during the primary  
46  
47 126 patient encounter without the camera physically contacting the patient. Digital  
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49 127 storage and transfer of TI is simple, utilizing a memory card in the TI device that can  
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51 128 be uploaded to a computer.  
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55 130 This study presents a prospective comparison of TI to CXR using a commercially  
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57 131 available thermal camera to determine the similarity of TI and CXR in the setting of  
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3 132 possible focal pneumonia and thus proof of concept and feasibility of TI to detect  
4 focal pneumonia.  
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10 135 Materials and Methods  
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14 137 Subjects: Participants came from the Emergency Department of Massachusetts  
15 General Hospital (Boston, MA). On admission to the Emergency Department, adult  
16 patients and families of children who had CXR included for evaluation of pneumonia  
17 were approached to discuss study participation. Written informed consent and, when  
18 applicable, participant assent was obtained from all participants. Enrollment  
19 occurred Monday - Friday, 7:00am - 11:00pm when research staff was available.  
20 Partners Human Research Committee approved the HIPPA compliant study protocol  
21 (#2013P001247).  
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32 146 In an initial Training Set, subjects were excluded if they had chronic lung disease,  
33 congestive heart failure, prior chest surgery or immunosuppression. In a subsequent  
34 TEST Set, these exclusions were not used. Patients had TI within 4 hours of CXR.  
35 Patients were male older than 28 days, or female older than 28 days and younger  
36 than 8 years. After age eight, only males were included because of concerns for  
37 modesty.  
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47 153 Forty-seven patients were enrolled. The first 15, comprising the Training Set, were  
48 not included as a part of the study's statistical assessment. These 15 cases provided  
49 a spectrum of results with 10 concordant for focal pneumonia, 2 concordant for no  
50 focal pneumonia, and 3 discordant for pneumonia. The remaining 32 subjects  
51 comprised the TEST Set. Analysis of the TEST Set included 31 patients (28 males, 3  
52 females), one patient had no usable thermal images. Patient age ranged from 10  
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3 159 months - 82 years (median = 50.0 years, (25th, 75th) quartiles = (11.5, 60.5  
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5 160 years), with 8 subjects  $\leq$  18 years and 23 subjects  $>$  18 years.  
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9 162 Imaging and interpretation: The radiologist interpreting CXR and TI (RHC) is an  
10 163 American Board of Radiology certified diagnostic radiologist and sub-certified  
11 164 pediatric radiologist with 40 years experience.  
12

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14  
15 166 CXRs were assessed in random order blinded to TI. If focal opacities were found, the  
16 167 lobe(s) were recorded (figure 1a). CXRs were taken in PA (posterior-anterior) and  
17 168 lateral projections (N = 19). If PA and lateral imaging could not be performed, a  
18 169 portable AP (anterior-posterior) image was acquired (N = 12).  
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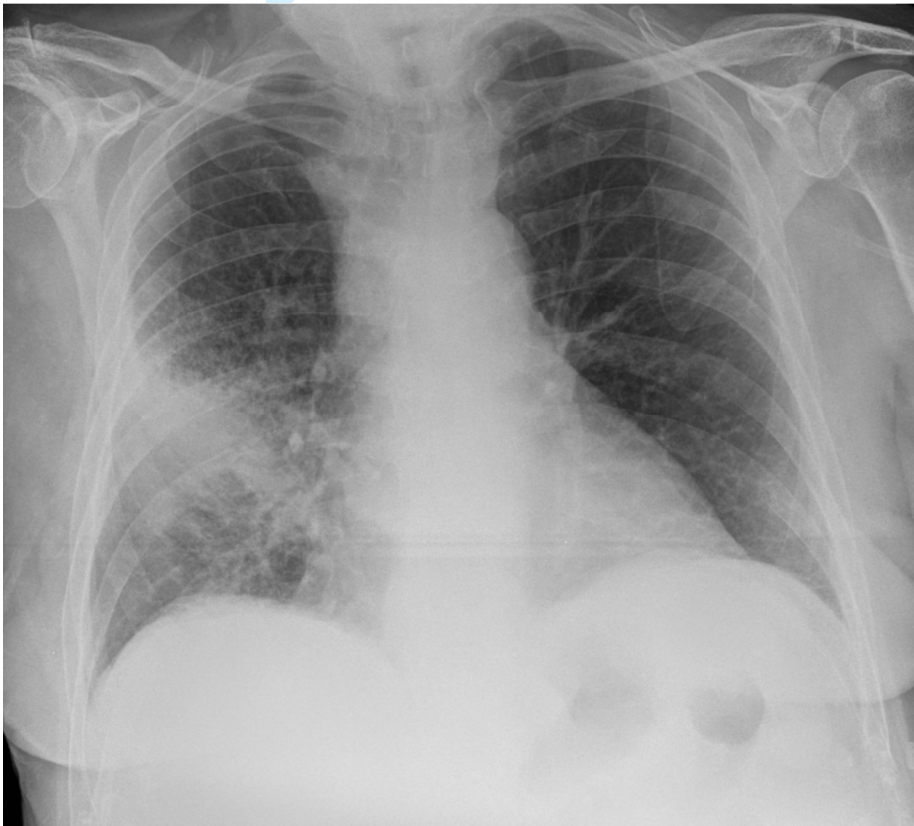
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28 171 TI of the chest were taken from the neck down, similar to CXR, with posterior and  
29 172 anterior views (N = 29). If only 1 view was obtainable, 1 patient had a posterior  
30 173 view and 1 an anterior view. TI were acquired with the commercially available FLIR  
31 174 i7 infrared thermal camera (flir.com). The subject was encompassed in the field of  
32 175 view; a "snapshot" was obtained so the patient's chest filled the field of view with the  
33 176 entire chest from side to side included from the level of the shoulders to bottom of  
34 177 the chest (or below). Patient to camera distance varied based on patient size.  
35 178 Subjects could be sitting or recumbent with the chest exposed. Clothing was  
36 179 removed from the chest prior to TI acquisition.  
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49 181 The camera used in this study has a resolution of 19,600 pixels detecting a  
50 182 temperature range  $-4^{\circ}$  Fahrenheit -  $482^{\circ}$  Fahrenheit ( $-20^{\circ}$  Celsius -  $250^{\circ}$  Celsius)  
51 183 with sensitivity to 0.1 degree Celsius. Images filled the 2.8 inch LCD TI screen. TI  
52 184 were interpreted while displayed on a desk top computer at a size comparable to the  
53 185 size of the CXR, filling roughly 50% of the computer monitor screen. TI image size  
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4 186 varies depending on the imaging device. TI stored in the camera's memory can be  
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6 187 uploaded to a computer and displayed at whatever size preferred.  
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10 189 TI were evaluated in random order blinded to CXR, recording any area(s) of  
11  
12 190 increased heat as upper, mid or lower lung segment and which side (figures 1  
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14 191 a,b,c). Following initial assessment of blinded TI and CXR, to shed light on possible  
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16 192 causes for TI/CXR discrepancies, cases with disagreement were reviewed in non-  
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18 193 blinded fashion, using comparison CXR when available.  
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46 Figure 1A  
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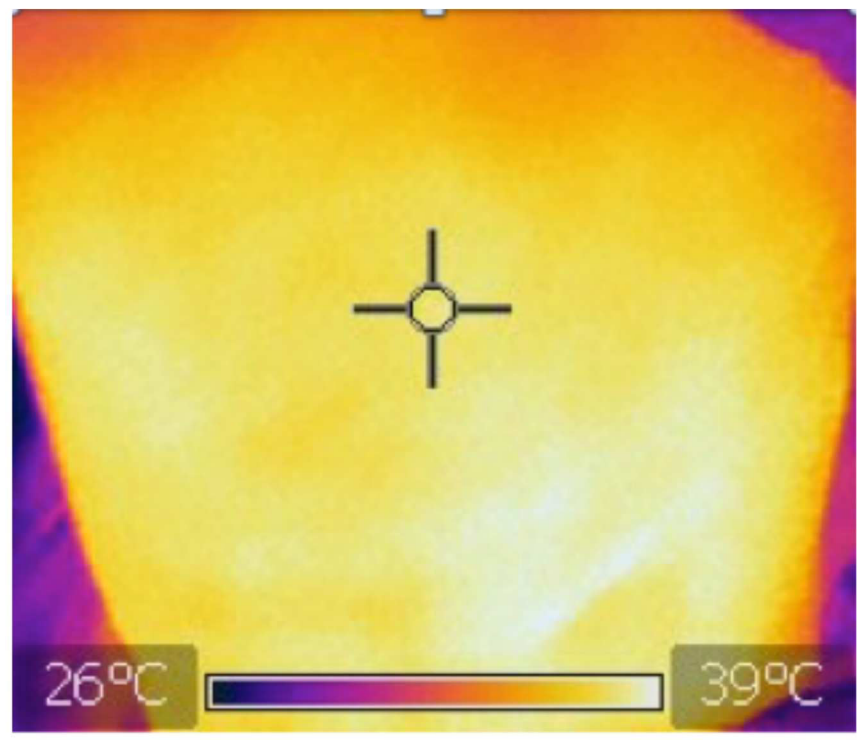
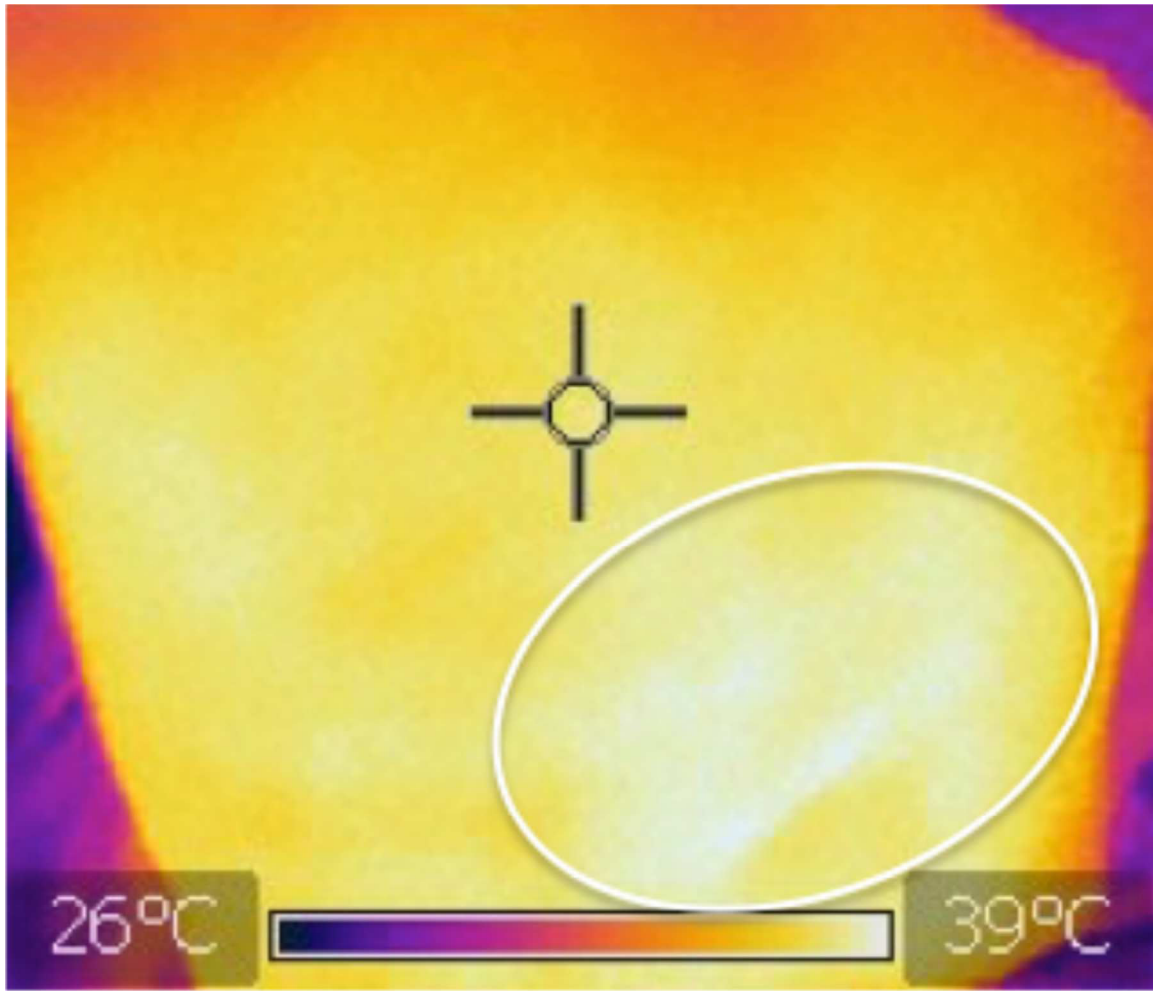


Figure1B

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Figure 1C

Legend:

Figure 1a: CXR shows an opacity in the right lung base consistent with pneumonia.

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3 221 Figure 1b: TI obtained shortly after the CXR (Figure 1a). The image is taken from  
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5 222 the patient's back so that the patient's right is on the viewer's right. There is an  
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7 223 area of increased heat (white area) in the right lung base concordant with the CXR.  
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11 225 Figure 1c: Same image as Figure 1b with the area of pneumonia (white area)  
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30 234 TI is similar to nuclear medicine imaging in that it is not the precise size,  
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32 235 configuration or margins that are of importance, but rather the temperature pattern  
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34 236 with presence or absence of focal areas of increased heat, "hot spots," that is  
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36 237 informative for focal pneumonia. Heat emanating from the patient's skin determines  
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38 238 the TI image. Generalized skin temperature does not affect TI recognition of a hot  
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40 239 spot. Since clothing recently removed from the chest might affect skin temperature  
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42 240 globally but not focally, it is unlikely that previously removed clothing would affect  
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44 241 recognition of a hot spot. Areas of symmetric increased heat were considered to  
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46 242 represent normal variation in heat pattern and areas of increased heat over the  
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48 243 neck, sternum, supraclavicular space, spine and axillae were determined to be  
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50 244 normal on the initial 15 training cases. Abdominal heat pattern is similar to that of  
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52 245 the chest without focal temperature changes relating to abdominal viscera. Unlike  
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54 246 CXR, TI does not require that patients hold their breath. Therefore, minor patient  
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56 247 motion will have minor, if any, effect on TI quality.  
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249 Statistical Methods: Paired data were constructed for each patient with CXR the  
250 standard for disease and TI the test variable. Each image was dichotomized as  
251 normal or showing focal pneumonia. TI sensitivity, specificity, positive predictive  
252 value and negative predictive value and their respective confidence intervals were  
253 estimated. Agreement between CXR and TI with patient age and sex was assessed  
254 using simple logistic regression models, as well as 2X2 contingency tables with age  
255 dichotomized as >18 years for adults and  $\leq$  18 years for children. Fisher's exact test  
256 was used to assess significance of correlation between age (or sex) and agreement  
257 between CXR and TI. Significance level of 0.05 was assumed.

258

## 259 Results

260

261 This study compares results of TI to contemporaneously performed CXR. For the  
262 overall cohort, five patients were identified as having focal pneumonia by CXR and  
263 26 not. For the pediatric cohort, there were 2 with focal pneumonia, 6 without by  
264 CXR.

265

266 Eleven cases were TI positive and CXR negative (false positives). One case was TI  
267 negative and CXR positive (false negative).

268

269 Table 1 summarizes TI sensitivity compared to CXR. TI agreed with CXR with  
270 pneumonia identified in the same anatomic location in 19 patients. Sensitivity,  
271 specificity, positive predictive value, negative predictive values and their  
272 corresponding confidence intervals (CI) are presented.

	True Positive	True Negative	False Positive	False Negative	Sensitivity (95% CI)	Specificity (95% CI)	Positive Predictive Value	Negative Predictive Value
TI vs blinded CXR (5 +ve, 26 -ve)	4	15	11	1	80.0% (29.9%, 98.9%)	57.7% (37.2%, 76.0%)	26.7% (8.9%, 55.2%)	93.8% (67.7%, 99.2%)

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274 Table 1: Sensitivity analysis of TI assuming the CXR as the outcome parameter.

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278 Relationship between TI and CXR agreement with patient demographics was  
 279 assessed using logistic regression models and simple contingency tables. There was  
 280 no significant correlation between modality agreement and patient age (treated as a  
 281 continuous variable or dichotomized as adult versus pediatric) or sex (age:  $p \geq 0.34$ ,  
 282 sex:  $p \geq 0.16$ ).

283

284 Since this is an exploratory proof of concept study the sample size is not based on  
 285 statistical power. In order to achieve a power of 0.80, with the conditions  
 286 encountered in this study, a power calculation showed 138 patients would be  
 287 required.

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289 To investigate causes for TI/CXR discrepancies, cases with disagreement were  
 290 reviewed in a non-blinded fashion, using prior and subsequent CXR (comparison

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3 291 images were not included in the blinded, original CXR assessments). This review of  
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5 292 discrepant cases is not included in the study's statistical analysis.  
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10 294 For the 11 false positive cases, comparison CXRs were available in three cases.  
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12 295 When CXR was reviewed with prior images, the interpretation was changed to focal  
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14 296 pneumonia (figure 2a,b,c) concordant with TI (figure 2d,e) in each instance. Follow-  
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16 297 up images provided no additional information. One case had diffuse changes of  
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18 298 cystic fibrosis, one with changes of chronic obstructive pulmonary disease and one  
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20 299 with low lung volumes.  
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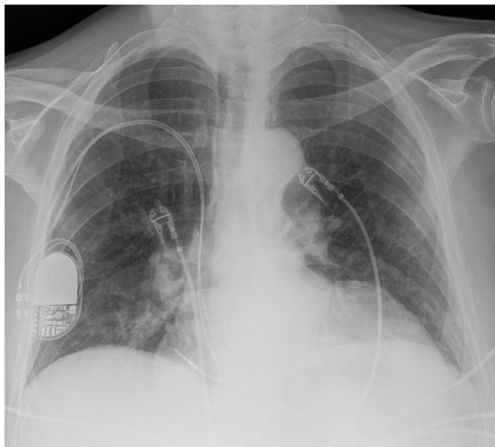
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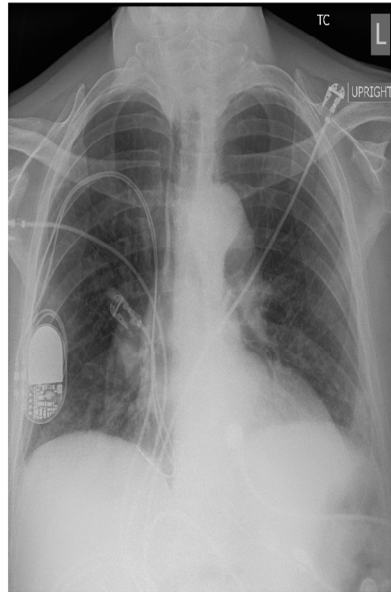


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Figure 2A

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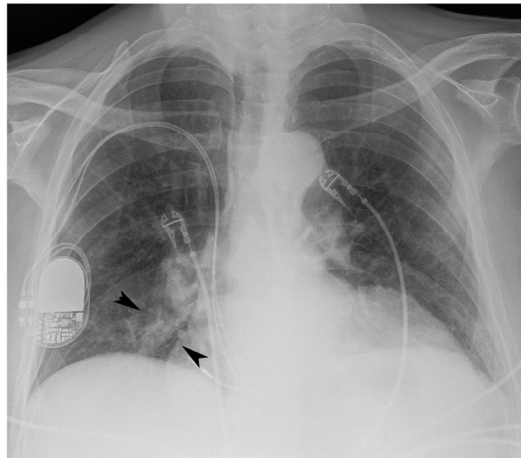


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Figure 2B

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Figure 2C

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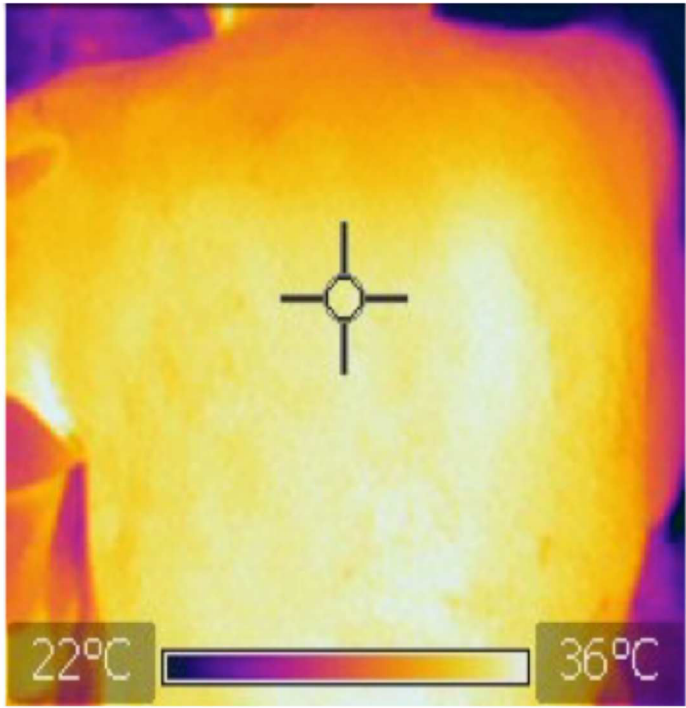


Figure 2D

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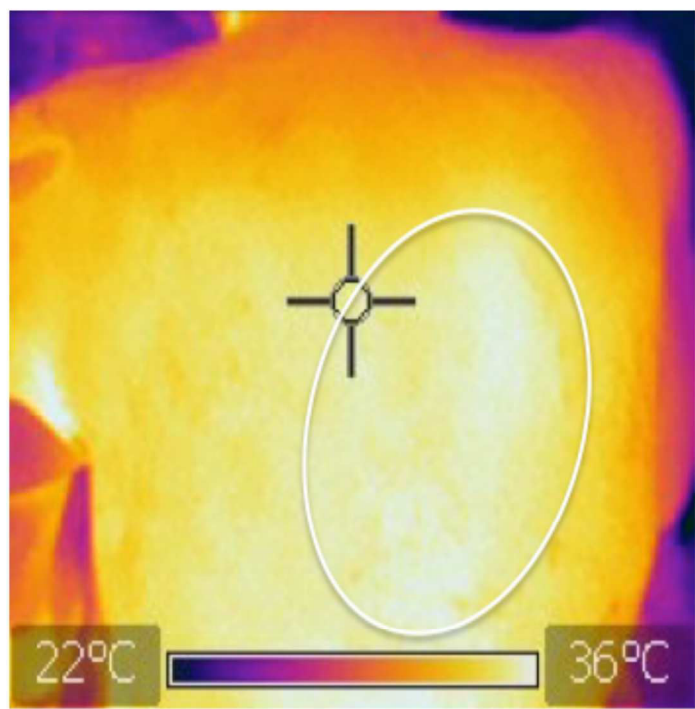


Figure 2E

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7 352 Figure 2a: Portable CXR taken in the Emergency Department during assessment for  
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9 353 acute pneumonia reveals low lung volumes and what was assumed to be resultant  
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11 354 crowding of pulmonary parenchyma in both lung bases medially. The interpretation  
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13 355 at that time was that there was no acute pneumonia.  
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18 357 Figure 2b: This CXR was performed 5 days before the CXR in Figure 2a. The lung  
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20 358 volumes are comparably low, but the small opacity in the right infrahilar region on  
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22 359 Figure 2a is not present. This indicates that there was a pneumonia in the right lung  
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24 360 base on the CXR in Figure 2a rather than normal crowding of lung tissue.  
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28 362 Figure 2c: Same image as figure 2a with the right infrahilar pneumonia indicated by  
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30 363 arrows.  
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34 365 Figure 2d: TI obtained shortly after the CXR shown in Figure 2a. The image is taken  
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36 366 from the patient's back so that the patient's right is on the viewer's right. There is  
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38 367 an area of increased heat (white area) in the right lung base concordant with that  
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40 368 seen in Figure 2a.  
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44 370 Figure 2e: Same image as Figure 2d with the area of pneumonia (white area)  
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46 371 encircled by an oval ring.  
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5 378 With knowledge of TI results, the CXR of one case was changed to a faint opacity,  
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7 379 consistent with focal pneumonia and in one case, there was the question of a very  
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9 380 subtle opacity, both concordant with the TI images.  
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14 382 Three CXR had what appeared to be atelectasis in regions of TI hot spots. In light of  
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16 383 the TI results, these may represent pneumonia. These opacities on CXR were, in one  
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18 384 case each, in the right upper lobe, left upper lobe and left lower lobe.  
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22 386 Three cases had no change in CXR interpretation.  
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26 388 The one false negative case had no change to TI or CXR interpretation.  
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30 390 There were no tumors, pulmonary edema or other abnormalities identified on CXR  
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32 391 that might affect TI results.  
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36 393 Non-blinded review produced no changes in interpretation of TI images.  
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41 395 Discussion  
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45 397 This study suggests that TI is sensitive and reasonably specific compared to the  
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47 398 outcome parameter of CXR in detecting focal pneumonia.  
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51 400 It is focal increased heat that is the indicator of focal pneumonia on TI. Thus any  
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53 401 bacterial organism (which organism cannot be determined) may be the culprit. Viral  
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55 402 pneumonias are generally diffuse and do not typically generate a focal pneumonia.  
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58 403 Some atypical pneumonias, such as mycoplasma, may have a focal consolidative  
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3 404 component which might be detected as a hot spot. It has been reported in a case  
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5 405 report that acute consolidative tuberculosis caused a TI hot spot but sub-acute  
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7 406 tuberculosis did not (21). It is not the precise lobar distribution but rather presence  
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9 407 or absence of a focal hot spot that is the informative aspect of TI.  
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13 409 The purpose of this study is not to determine whether TI or CXR is superior in  
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15 410 detecting pneumonia but to assess how well TI and CXR agree in detecting a focal  
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17 411 consolidation. This is in the context of CXR being the most widely utilized standard  
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19 412 for diagnosis of pneumonia (19, 20, 24-29), including studies assessing effectiveness  
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21 413 of the WHO clinical diagnostic criteria (29). Ultrasound is the only other point of care  
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23 414 imaging procedure widely studied for diagnosis of pneumonia and in virtually all of its  
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25 415 validation studies it is compared to CXR (26-28). While clinical signs and symptoms  
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27 416 have been utilized, collecting accurate data and correlation with the ultimate  
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29 417 diagnosis of pneumonia is inconsistent (30). However, it is not the purpose of this  
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31 418 study to assess the accuracy of imaging to detect pneumonia as compared to the  
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33 419 clinical diagnosis. Ultimately, other methodologies such as inflammatory markers  
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35 420 may play a role, but currently these are in relatively early stages of development.  
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39 422 Accuracy of CXR in determining the presence of focal pneumonia will vary depending  
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41 423 on quality of imaging and experience of the observer, as is true for TI. Although  
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43 424 computerized tomography (CT) has greater accuracy in detecting pneumonia than  
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45 425 CXR (31-32), CT cannot be used as routine imaging for pneumonia because of  
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47 426 concerns of radiation exposure and cost (29).  
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51 428 There was only one false negative in the cohort of 31 patients with 11 false positives  
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53 429 (sensitivity = 0.80, specificity = 0.58). Thus the ability of TI to accurately detect  
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55 430 focal pneumonia (as determined by CXR), in this cohort was high. For a screening  
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3 431 test, this ability to not miss focal pneumonia is the most critical criterion. The higher  
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5 432 rate of false positives would lead to either over treating or further testing in a limited  
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7 433 number of patients, which, although important, is a less critical issue.

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9 434 The changes in CXR interpretation on non-blinded review of discrepant TI/CXR  
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11 435 revealed the following. 1) TI had hot spots in cases where CXR findings were initially  
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13 436 not definitive for focal pneumonia (N = 5). For two, CXR diagnosis was confounded  
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15 437 by pre-existing chronic lung diseases and in one by shallow inflation. For two others,  
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17 438 the suggestion of focal pneumonia on CXR was too subtle for definitive diagnosis. 2)  
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19 439 TI revealed hot spots in cases where the blinded CXR suggested atelectasis (N = 3).  
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21 440 This suggests that TI may be able to detect focal pneumonia in cases where pre-  
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23 441 existing lung disease or imaging technique confound the diagnosis on CXR or when  
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25 442 diagnosis on CXR is too subtle to be convincing (as possibly with early onset or  
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27 443 resolving focal pneumonia). TI may be able to differentiate between focal  
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29 444 pneumonia and atelectasis.

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31 445 These findings suggest TI may be comparable to CXR in recognizing focal  
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33 446 pneumonia. Relatively low cost and portability of thermal cameras, some of which  
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35 447 can be used with mobile phones, potentially enable TI as a point of care screening  
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37 448 tool for focal pneumonia. Other advantages include minimal training to perform  
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39 449 images, lack of ionizing radiation exposure, off-site interpretation of digitized images  
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41 450 and possible software interpretation algorithms. Lack of physical contact with the  
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43 451 patient enhances infection control. Possible additional uses include following  
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45 452 progression of disease in combination with other modalities such as respiratory rate  
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47 453 and oximetry.

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51 455 Limitations of TI include learning to interpret TI, presence of prior disease affecting  
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53 456 TI and the possibility that increased adiposity may interfere with its accuracy.

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3 458 Conclusions  
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7 460 This feasibility study confirms proof of concept that TI can demonstrate focal  
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9 461 pneumonia. Therefore, these findings support further investigation with larger trials  
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11 462 of patients that will be adequately powered to robustly assess the similarity between  
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13 463 TI and the outcome parameter. This technology is potentially most useful in  
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15 464 resource-limited environments where pneumonia is the second most common cause  
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17 465 of death in young children and where CXR equipment and expert readers are  
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19 466 unavailable (33). It also could be of benefit in high throughput healthcare settings,  
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21 467 such as emergency departments or busy doctors' offices and rural areas where  
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23 468 access to CXR is limited.  
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19 477 **Contributor ship Statement:**

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23 479 Specific Contributions from each author

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25 480

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30 483 interpretation of data, and drafting the work and revising it critically

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4 501 work critically

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45 521 Competing Interests

46  
47 522 None of the authors have conflicts of interest to report relating to this work

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53 525 organisations that might have an interest in the submitted work in the previous three years; no other  
54 526 relationships or activities that could appear to have influenced the submitted work."

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659 Tables

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	True Positive	True Negative	False Positive	False Negative	Sensitivity (95% CI)	Specificity (95% CI)	Positive Predictive Value	Negative Predictive Value
TI vs blinded CXR (5 +ve, 26 -ve)	4	15	11	1	80.0% (29.9%, 98.9%)	57.7% (37.2%, 76.0%)	26.7% (8.9%, 55.2%)	93.8% (67.7%, 99.7%)

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664 Table 1: Sensitivity analysis of TI assuming the CXR as the outcome parameter.

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## Figure Legends

Figure 1a: CXR shows an opacity in the right lung base consistent with pneumonia.

Figure 1b: TI obtained shortly after the CXR (Figure 1a). The image is taken from the patient's back so that the patient's right is on the viewer's right. There is an area of increased heat (white area) in the right lung base concordant with the CXR.

Figure 1c: Same image as Figure 1b with the area of pneumonia (white area) encircled by an oval ring.

Figure 2a: Portable CXR taken in the Emergency Department during assessment for acute pneumonia reveals low lung volumes and what was assumed to be resultant crowding of pulmonary parenchyma in both lung bases medially. The interpretation at that time was that there was no acute pneumonia.

Figure 2b: This CXR was performed 5 days before the CXR in Figure 2a. The lung volumes are comparably low, but the small opacity in the right infrahilar region on Figure 2a is not present. This indicates that there was a pneumonia in the right lung base on the CXR in Figure 2a rather than normal crowding of lung tissue.

Figure 2c: Same image as figure 2a with the right infrahilar pneumonia indicated by arrows.

Figure 2d: TI obtained shortly after the CXR shown in Figure 2a. The image is taken from the patient's back so that the patient's right is on the viewer's right. There is

1  
2  
3 an area of increased heat (white area) in the right lung base concordant with that  
4  
5 seen in Figure 2a.  
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10 Figure 2e: Same image as Figure 2d with the area of pneumonia (white area)  
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12 encircled by an oval ring.  
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These are the figures 1 a, b, c

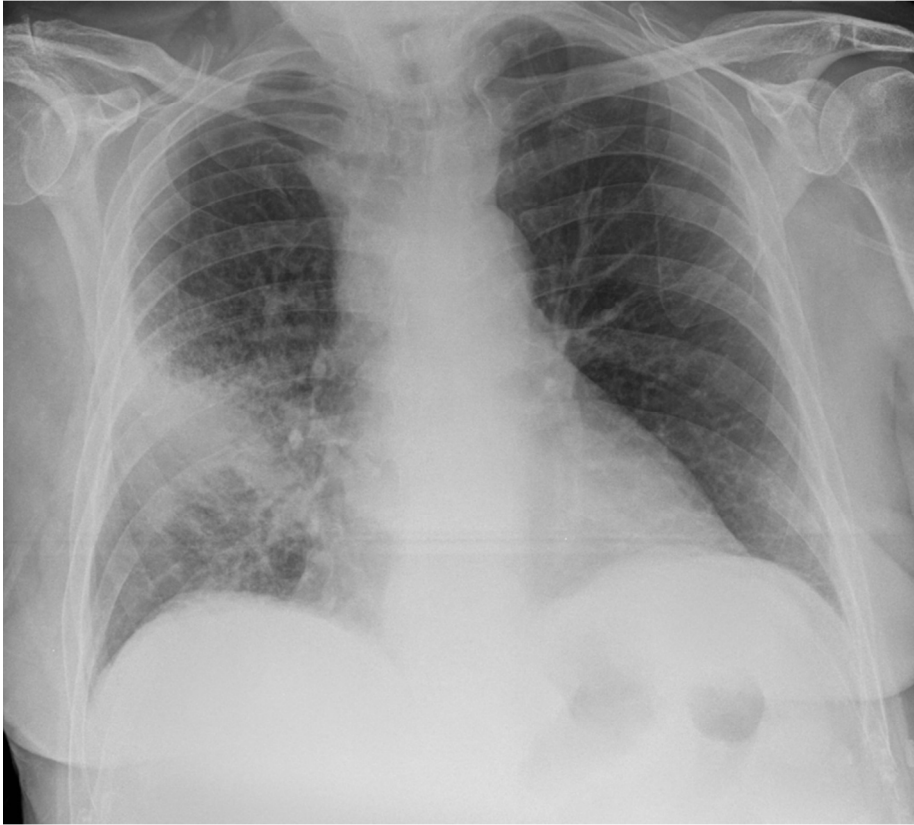


Figure 1A

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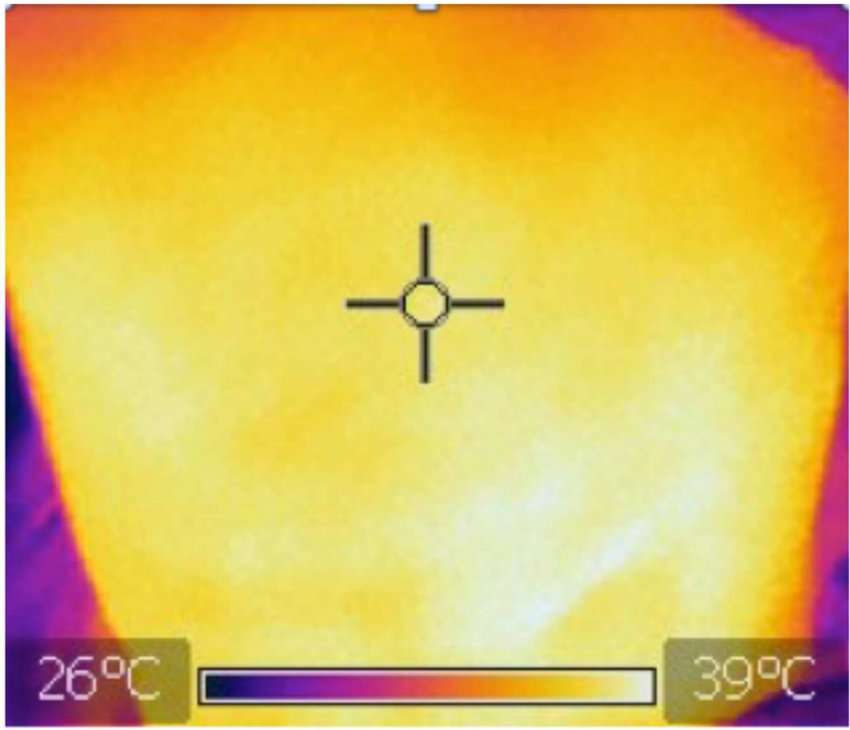
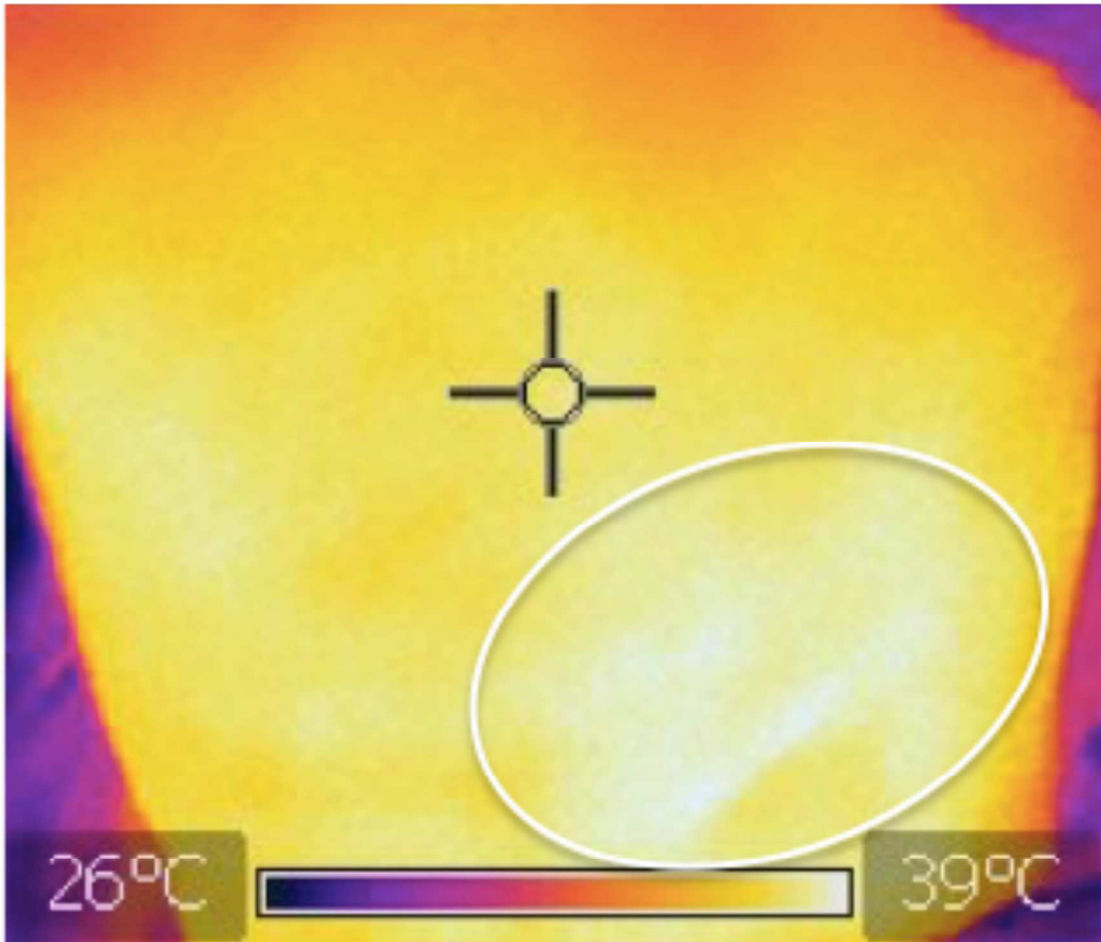


Figure1B

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1  
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10 Legend:

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13 Figure 1a: CXR shows an opacity in the right lung base consistent with  
14 pneumonia.  
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21 Figure 1b: TI obtained shortly after the CXR (Figure 1a). The image is taken  
22 from the patient's back so that the patient's right is on the viewer's right.  
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24 There is an area of increased heat (white area) in the right lung base  
25 concordant with the CXR.  
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33 Figure 1c: Same image as Figure 1b with the area of pneumonia (white area)  
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Figures 2 a – e

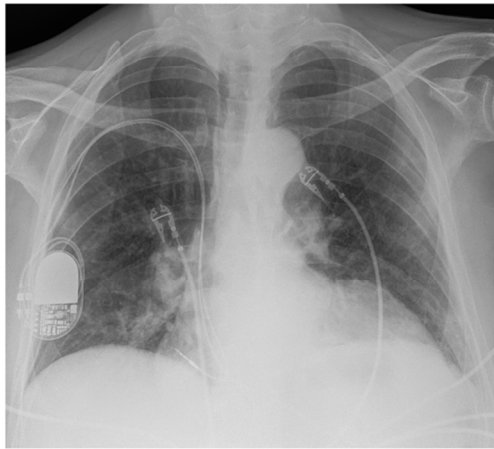


Figure 2A

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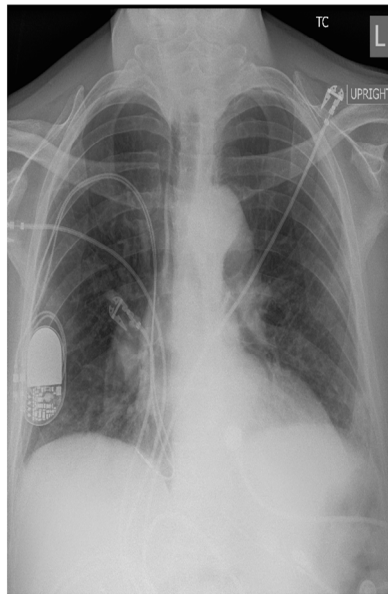


Figure 2B

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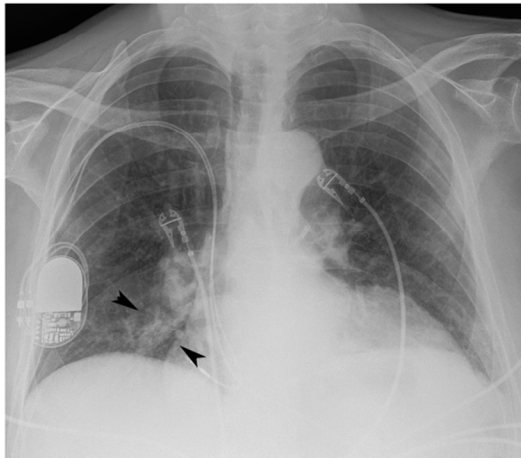


Figure 2C

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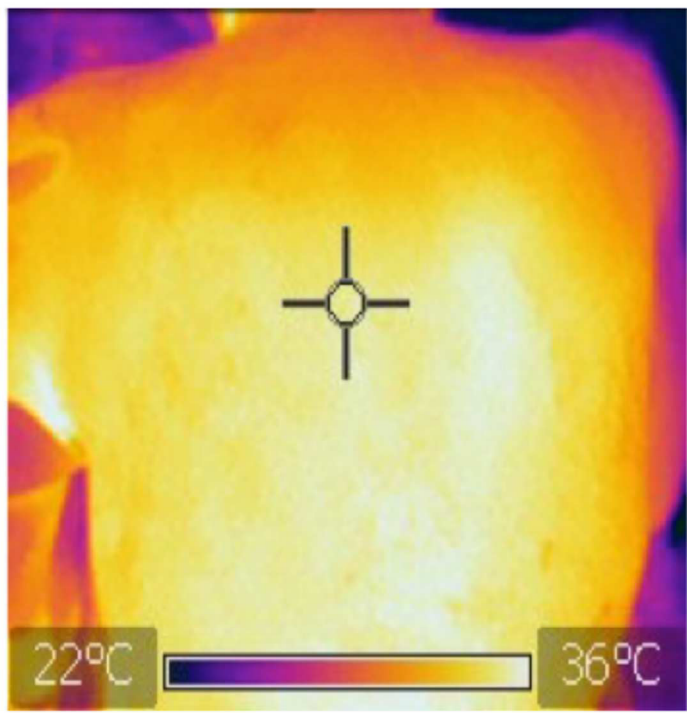


Figure 2D

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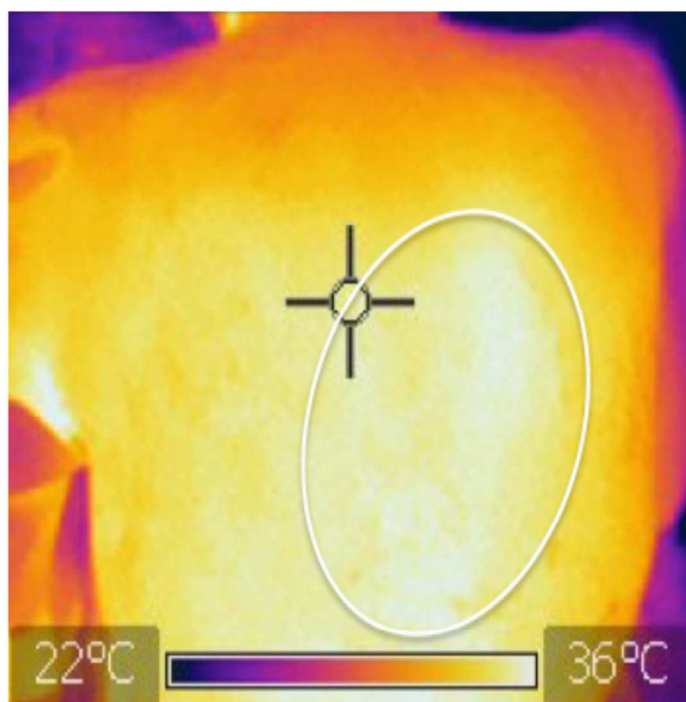


Figure 2E

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### Legend

Figure 2a: Portable CXR taken in the Emergency Department during assessment for acute pneumonia reveals low lung volumes and what was assumed to be resultant crowding of pulmonary parenchyma in both lung bases medially. The interpretation at that time was that there was no acute pneumonia.

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Figure 2b: This CXR was performed 5 days before the CXR in Figure 2a. The lung volumes are comparably low, but the small opacity in the right infrahilar region on Figure 2a is not present. This indicates that there was a pneumonia in the right lung base on the CXR in Figure 2a rather than normal crowding of lung tissue.

Figure 2c: Same image as figure 2a with the right infrahilar pneumonia indicated by arrows.

Figure 2d: TI obtained shortly after the CXR shown in Figure 2a. The image is taken from the patient's back so that the patient's right is on the viewer's right. There is an area of increased heat (white area) in the right lung base concordant with that seen in Figure 2a.

Figure 2e: Same image as Figure 2d with the area of pneumonia (white area) encircled by an oval ring.

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## Items to include when reporting a randomized trial in a journal or conference abstract

Item	Description	Reported on line number
Title	Identification of the study as randomized	1
Authors *	Contact details for the corresponding author	4 - 7
Trial design	Description of the trial design (e.g. parallel, cluster, non-inferiority)	162; 245
Methods		
Participants	Eligibility criteria for participants and the settings where the data were collected	133, 142-147
Interventions	Interventions intended for each group	149-151, 162-172;
Objective	Specific objective or hypothesis	91-92; 126- 129; 257
Outcome	Clearly defined primary outcome for this report	185-189
Randomization	How participants were allocated to interventions	133; 149
Blinding (masking)	Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment	185-189
Results		
Numbers randomized	Number of participants randomized to each group	149
Recruitment	Trial status	
Numbers analysed	Number of participants analysed in each group	149
Outcome	For the primary outcome, a result for each group and the estimated effect size and its precision	185, 265, 290
Harms	Important adverse events or side effects	
Conclusions	General interpretation of the results	424-442
Trial registration	Registration number and name of trial register	NA
Funding	Source of funding	Funding: The Bacca Foundation and the Consortium for Affordable Medical Technologies (CAMTech) (Fund # is 223707)

*\*this item is specific to conference abstracts*

# BMJ Open

## Similarity of Chest X-ray and Thermal Imaging of Focal Pneumonia: A Randomized Proof of Concept Study at a Large Urban Teaching Hospital

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-017964.R1
Article Type:	Research
Date Submitted by the Author:	19-Aug-2017
Complete List of Authors:	Wang, Linda; Massachusetts General Hospital, Emergency Medicine and Pediatric Global Health Cleveland, Robert; Children's Hospital Boston, Radiology Binder, William; Brown University, Emergency Medicine Zwerdling, Robert; university of massachusetts, radiology Stamoulis, Caterina; children's hospital of boston, adolescent and young adult research Ptak, Thomas; Emory University Hospital, Radiology Sherman, Mindy; Massachusetts General Hospital, Emergency Medicine Haver, Kenan; Children's Hospital Boston, Pulmonary and Respiratory Diseases Sagar, Pallavi; Massachusetts General Hospital, Radiology Hibberd, Patricia; Boston Medical Center, Department of Global Health
<b>Primary Subject Heading</b>:	Radiology and imaging
Secondary Subject Heading:	Global health, Respiratory medicine, Infectious diseases, Paediatrics
Keywords:	Paediatric radiology < PAEDIATRICS, Chest imaging < RADIOLOGY & IMAGING, Respiratory infections < THORACIC MEDICINE, Diagnostic radiology < RADIOLOGY & IMAGING

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Manuscripts

1 Similarity of Chest X-ray and Thermal Imaging of Focal Pneumonia: A randomized  
2 proof of concept study at a large urban teaching hospital.

3  
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6 Thomas Ptak, M.D., PhD<sup>5</sup>, Mindy Sherman, M.D.<sup>6</sup>, Kenan Haver M.D.<sup>7</sup>, Pallavi Sagar,  
7 M.D.<sup>9</sup>, Patricia Hibberd, M.D., PhD.<sup>10</sup>

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10 Boston Children's Hospital, Boston, MA: 2, 4, 7

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12 Emory University Hospital, Atlanta, GA: 5

13 Brown University Medical School, Providence, RI: 8

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24 38 ABSTRACT  
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28 40 Objective: To determine the similarity of thermal imaging (TI) to chest x-ray (CXR)  
29 41 in the setting of focal consolidative pneumonia.  
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34 43 Setting: A large, 973 bed teaching hospital in Boston, Massachusetts  
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38 45 Participants: 47 patients enrolled, 15 in a training set, 32 in a test set. Age range  
39 46 10 months – 82 years (median = 50 years)  
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44 48 Materials and Methods: Subjects received CXR with subsequent TI within 4 hours of  
45 49 each other. CXR and TI were assessed in blinded random order. Presence of focal  
46 50 opacity (pneumonia) on CXR, the outcome parameter, was recorded. For TI,  
47 51 presence of area(s) of increased heat (pneumonia) was recorded. Fisher's exact test  
48 52 was used to assess the significance of the correlations of positive findings in the  
49 53 same anatomic region.  
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3 55 Results: With TI compared to the CXR (the outcome parameter), sensitivity was  
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5 56 80.0% (Confidence intervals (CI): [29.9%, 98.9%], specificity was 57.7% (CI:  
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7 57 [37.2%, 76.0%]). Positive predictive value of TI was 26.7% (CI: [8.9%, 55.2%])  
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10 58 and its negative predictive value was 93.8% (CI: [67.7%, 99.7%]).  
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14 60 Conclusions: This feasibility study confirms proof of concept that chest TI is  
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16 61 consistent with CXR in suggesting similarly localized focal pneumonia with high  
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18 62 sensitivity and negative predictive value. Further investigation of TI as a point of  
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20 63 care imaging modality is warranted.  
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24 65 Strengths and Limitations:  
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28 67 Strengths:

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30 68 • Proof of concept suggesting that Thermal Imaging (TI) is a valid,  
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32 69 innovative, and inexpensive technology useful for diagnosing bacterial  
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34 70 pneumonia  
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36 71 • Proof of concept suggesting that Thermal Imaging (TI) is a rapid  
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38 72 means of diagnosing focal pneumonia in high throughput settings  
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40 73 • Proof of concept suggesting that Thermal Imaging (TI) is a valid and  
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42 74 innovative technology useful in diagnosing pneumonia in resource  
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5 79 be definitive and cannot replace chest xray for detecting focal  
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10 81 • As this is a proof of concept study, limitations of the technology have  
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12 82 not been fully discerned, and at present include adipose tissue and  
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14 83 interpretation, but may include other concerns which will require  
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16 84 higher numbers of patients enrolled.  
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20 85 Word Count: 3116  
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23 86• Data Sharing: There are no additional unpublished data from the study. Data are  
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25 87 available to any researcher who is interested in the data, and will be able to be  
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27 88 accessed through Dyad and/or through correspondence with the contributing  
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29 89 authors.  
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## 33 92 Introduction 34 35 93

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37 94 This study investigates the degree to which thermal imaging (TI) and chest x-ray  
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39 95 (CXR) agree in detecting similarly localized focal pneumonia. Often a clinically  
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41 96 challenging diagnosis, bacterial pneumonia remains a major cause of morbidity and  
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43 97 mortality worldwide, particularly in under-resourced environments (1-3). Expert  
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45 98 panels, including the World Health Organization (WHO), have formulated algorithms  
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47 99 to enhance clinical accuracy (4), typically focusing on aspects of the medical history  
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49 100 and physical examination to determine the likelihood of bacterial pneumonia. Despite  
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51 101 having these algorithms, CXR is generally performed to confirm the diagnosis in  
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53 102 severe infections (5-16). If TI results are similar to CXR, it might substitute for CXR  
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55 103 when CXR is not available. In resource-limited environments, where 2/3 of the  
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3 104 world's population has no access to diagnostic imaging (17-18), the potential use of  
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5 105 TI in point of care screening could aid decision making to treat for pneumonia.  
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7 106 Point of care imaging utilizing ultrasonography to diagnose pneumonia is attracting  
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9 107 interest (19-20). However, ultrasonography requires costly equipment and specific  
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11 108 expertise for image acquisition and interpretation.  
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16 110 Anecdotal reports suggest that TI has potential for detecting pneumonia (21-22).  
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18 111 These case reports and methodologies have not been subjected to systematic  
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20 112 blinded assessment. In this initial proof of concept investigation, we compared TI to  
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22 113 CXR in patients suspected of having acute pneumonia.  
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26 115 With recent advances in infrared technology and increasing use assessing home heat  
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28 116 loss, low-cost thermal cameras have become available, currently costing as little as  
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30 117 \$200-\$300 (Flir.com). Installation of shielded radiographic rooms can cost hundreds  
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32 118 of thousands of dollars. Portable x-ray units capable of performing CXR can cost as  
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34 119 little as \$600-\$800 (dotmed.com). If uninsured, patient cost of a CXR in the US is  
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36 120 \$200-\$400 or, if insured, a co-pay of \$10-\$50 (23).  
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40 122 For TI there are no additional costs beyond cost of the camera. TI cameras are  
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42 123 portable and operate with rechargeable batteries. TI is essentially identical to taking  
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44 124 a "snap and shoot" photograph and can be done in seconds during the primary  
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46 125 patient encounter without the camera physically contacting the patient. Digital  
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48 126 storage and transfer of TI is simple, utilizing a memory card in the TI device that can  
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50 127 be uploaded to a computer.  
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55 129 This study presents a prospective comparison of TI to CXR using a commercially  
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57 130 available thermal camera to determine the similarity of TI and CXR in the setting of  
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3 131 possible focal pneumonia and thus proof of concept and feasibility of TI to detect  
4 focal pneumonia.  
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10 134 Materials and Methods  
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14 136 Subjects: Participants came from the Emergency Department of Massachusetts  
15 General Hospital (Boston, MA). On admission to the Emergency Department, adult  
16 137 patients and families of children who had CXR included for evaluation of pneumonia  
17 138 were approached to discuss study participation. Written informed consent and, when  
18 139 applicable, participant assent was obtained from all participants. Enrollment  
19 140 occurred Monday - Friday, 7:00am - 11:00pm when research staff was available.  
20 141 Partners Human Research Committee approved the HIPPA compliant study protocol  
21 142 (#2013P001247).  
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26 145 In an initial Training Set, subjects were excluded if they had chronic lung disease,  
27 146 congestive heart failure, prior chest surgery or immunosuppression. In a subsequent  
28 147 TEST Set, these exclusions were not used. Patients had TI within 4 hours of CXR.  
29 148 Patients were male older than 28 days, or female older than 28 days and younger  
30 149 than 8 years. After age eight, only males were included because of concerns for  
31 150 modesty.  
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35 152 Forty-seven patients were enrolled. The first 15, comprising the Training Set, were  
36 153 not included as a part of the study's statistical assessment. These 15 cases provided  
37 154 a spectrum of results with 10 concordant for focal pneumonia, 2 concordant for no  
38 155 focal pneumonia, and 3 discordant for pneumonia. The remaining 32 subjects  
39 156 comprised the TEST Set. Analysis of the TEST Set included 31 patients (28 males, 3  
40 157 females), one patient had no usable thermal images. Patient age ranged from 10  
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3 158 months - 82 years (median = 50.0 years, (25th, 75th) quartiles = (11.5, 60.5  
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5 159 years), with 8 subjects  $\leq$  18 years and 23 subjects  $>$  18 years.  
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9 161 Imaging and interpretation: The radiologist interpreting CXR and TI (RHC) is an  
10 162 American Board of Radiology certified diagnostic radiologist and sub-certified  
11 163 pediatric radiologist with 40 years experience.  
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18 165 CXRs were assessed in random order blinded to TI. If focal opacities were found, the  
19 166 lobe(s) were recorded (figure 1a). The lobes involved were precisely determined  
20 167 with posterior-anterior (PA) and lateral examinations. When only a portable  
21 168 anterior-posterior (AP) image could be obtained, the lobe(s) involved was  
22 169 determined by lung zone and presence/absence of silhouetting of the mediastinum.  
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25 170 CXRs were taken in PA and lateral projections (N = 19). If PA and lateral imaging  
26 171 could not be performed, because of clinical care requirements, a portable AP image  
27 172 was acquired (N = 12).  
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36 173  
37 174 TI of the chest were taken from the neck down, similar to CXR, with both posterior  
38 175 and anterior views whenever possible (N = 29). If a patient was too ill to be  
39 176 positioned for two views only 1 view was obtained. Depending on the patients'  
40 177 condition and preferred position, 1 patient had a posterior view and 1 an anterior  
41 178 view. Oblique images were not obtained since TI interpretation depends on  
42 179 assessment of asymmetric heat distribution. TI were acquired with the commercially  
43 180 available FLIR i7 infrared thermal camera (flir.com). The subject was encompassed  
44 181 in the field of view; a "snapshot" was obtained so the patient's chest filled the field of  
45 182 view with the entire chest from side to side included from the level of the shoulders  
46 183 to bottom of the chest (or below). Patient to camera distance varied based on patient  
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3 184 size. Subjects could be sitting or recumbent with the chest exposed. Clothing was  
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5 185 removed from the chest prior to TI acquisition.  
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10 187 The camera used in this study has a resolution of 19,600 pixels detecting a  
11  
12 188 temperature range -4° Fahrenheit - 482° Fahrenheit (-20° Celsius - 250° Celsius)  
13  
14 189 with sensitivity to 0.1 degree Celsius. Images filled the 2.8 inch LCD TI screen. TI  
15  
16 190 were interpreted while displayed on a desk top computer at a size comparable to the  
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18 191 size of the CXR, filling roughly 50% of the computer monitor screen. TI image size  
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20 192 varies depending on the imaging device. TI stored in the camera's memory can be  
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22 193 uploaded to a computer and displayed at whatever size preferred.  
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26 195 TI were evaluated in random order blinded to CXR. Any area(s) of increased heat  
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28 196 were recorded as upper, mid or lower lung zone, and identified as in the right or left  
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30 197 lung. (figures 1,2,3). Following initial assessment of blinded TI and CXR, to shed  
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32 198 light on possible causes for TI/CXR discrepancies, cases with disagreement were  
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34 199 reviewed in non-blinded fashion, using prior CXR when available.  
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7 213 Figure 1: CXR shows an opacity in the right lung base consistent with pneumonia.

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11 215 Figure 2: TI obtained shortly after the CXR (Figure 1). The image is taken from the  
12 patient's back so that the patient's right is on the viewer's right. There is an area of  
13 increased heat (white area) in the right lung base concordant with the CXR.  
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19 219 Figure 3: Same image as Figure 2 with the area of pneumonia (white area) encircled  
20 by an oval ring.  
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38 228 TI is similar to nuclear medicine imaging in that it is not the precise size,  
39 configuration or margins that are of importance, but rather the temperature pattern  
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41 229 with presence or absence of focal areas of increased heat, "hot spots," that is  
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43 230 informative for focal pneumonia. Heat emanating from the patient's skin determines  
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45 231 the TI image. Generalized skin temperature does not affect TI recognition of a hot  
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47 232 spot. Since clothing recently removed from the chest might affect skin temperature  
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49 233 globally but not focally, it is unlikely that previously removed clothing would affect  
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51 234 recognition of a hot spot. Areas of symmetric increased heat were considered to  
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53 235 represent normal variation in heat pattern and areas of increased heat over the  
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55 236 neck, sternum, supraclavicular space, spine and axillae were determined to be  
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3 238 normal on the initial 15 training cases. Abdominal heat pattern is similar to that of  
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5 239 the chest without focal temperature changes relating to abdominal viscera. Unlike  
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7 240 CXR, TI does not require that patients hold their breath. Therefore, minor patient  
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9 241 motion will have minor, if any, effect on TI quality.  
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14 243 Statistical Methods: Paired data were constructed for each patient with CXR the  
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16 244 standard for disease and TI the test variable. Each image was dichotomized as  
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18 245 normal or showing focal pneumonia. TI sensitivity, specificity, positive predictive  
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20 246 value and negative predictive value and their respective confidence intervals were  
21  
22 247 estimated. Agreement between CXR and TI (modeled as a binary outcome with  
23  
24 248 agreement = 1 and disagreement = 0) and as a function of with patient age and sex  
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26 249 was assessed using simple logistic regression models, as well as 2X2 contingency  
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28 250 tables with age dichotomized as >18 years for adults and ≤ 18 years for children.  
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30 251 Fisher's exact test was used to assess significance of correlation between age (or  
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32 252 sex) and agreement between CXR and TI. A significance level of 0.05 was assumed.  
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## 36 254 Results

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41 256 This study compares results of TI to contemporaneously performed CXR. For the  
42  
43 257 overall cohort, five patients were identified as having focal pneumonia by CXR and  
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45 258 26 not. For the pediatric cohort, there were 2 with focal pneumonia, 6 without by  
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47 259 CXR.  
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51 261 Eleven cases were TI positive and CXR negative (false positives). One case was TI  
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53 262 negative and CXR positive (false negative).  
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264 Table 1 summarizes TI sensitivity compared to CXR. TI agreed with CXR with  
 265 pneumonia identified in the same anatomic location in 19 patients. Sensitivity,  
 266 specificity, positive predictive value, negative predictive values and their  
 267 corresponding confidence intervals (CI) are presented.

	True Positive	True Negative	False Positive	False Negative	Sensitivity (95% CI)	Specificity (95% CI)	Positive Predictive Value	Negative Predictive Value
TI vs blinded CXR (15 +ve, 26 -ve)	4	15	11	1	80.0% (29.9%, 98.9%)	57.7% (37.2%, 76.0%)	26.7% (8.9%, 55.2%)	93.8% (67.7%, 99.7%)

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269 Table 1: Sensitivity analysis of TI assuming the CXR as the outcome parameter. 95%  
 270 Confidence intervals (CI) are included for all parameters.

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273 The relationship between TI and CXR agreement with patient demographics was  
 274 assessed using logistic regression models and simple contingency tables. There was  
 275 no significant correlation between modality agreement and patient age (treated as a  
 276 continuous variable or dichotomized as adult versus pediatric) or sex (age:  $p = 0.3$   
 277 [95% CI for the regression coefficient = (-0.01, 0.004)]; sex:  $p = 0.16$  [95% CI =  
 278 (-0.16, 1.05)]).

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280 Since this is an exploratory proof of concept study the sample size is not based on  
 281 statistical power. In order to achieve a power of 0.80, with the conditions

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3 282 encountered in this study, a power calculation showed 138 patients would be  
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5 283 required.  
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9 285 To investigate causes for TI/CXR discrepancies, cases with disagreement were  
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11 286 reviewed in a non-blinded fashion, using prior and subsequent CXR (comparison  
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13 287 images were not included in the blinded, original CXR assessments). This review of  
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15 288 discrepant cases is not included in the study's statistical analysis.  
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20 290 For the 11 false positive TI cases, prior CXRs were available in only three cases.  
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22 291 Each of these 3 cases had diffuse findings confounding CXR interpretation. One had  
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24 292 diffuse changes of cystic fibrosis, one had changes of chronic obstructive pulmonary  
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26 293 disease and one had low lung volumes. When CXR was reviewed with prior CXR, the  
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28 294 CXR interpretation was changed to focal pneumonia (figure 4,5,6) concordant with TI  
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30 295 (figure 7,8) in each instance. Follow-up images provided no additional information.  
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32 296 (INSERT FIGURES 4, 5, 6, 7, 8)  
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7 311 Figure 4: Portable CXR taken in the Emergency Department during assessment for  
8 acute pneumonia reveals low lung volumes and what was assumed to be resultant  
9 crowding of pulmonary parenchyma in both lung bases medially. The interpretation  
10 at that time was that there was no acute pneumonia.  
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15 315  
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17 316 Figure 5: This CXR was performed 5 days before the CXR in Figure 4. The lung  
18 volumes are comparably low, but the small opacity in the right infrahilar region on  
19 Figure 4 is not present. This indicates that there was a pneumonia in the right lung  
20 base on the CXR in Figure 4 rather than normal crowding of lung tissue.  
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28 321 Figure 6: Same image as figure 4 with the right infrahilar pneumonia indicated by  
29 arrows.  
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34 324 Figure 7: TI obtained shortly after the CXR shown in Figure 4. The image is taken  
35 from the patient's back so that the patient's right is on the viewer's right. There is  
36 an area of increased heat (white area) in the right lung base concordant with that  
37 seen in Figure 4.  
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45 by an oval ring.  
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53 333 For 2 other cases, knowledge of TI findings resulted in a change in the CXR  
54 interpretation. For one case, the CXR interpretation was changed to a faint opacity,  
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3 335 consistent with focal pneumonia and in one case, there was the question of a very  
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5 336 subtle opacity, both concordant with the TI images.  
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10 338 Three other CXRs had what appeared to be atelectasis in regions of TI hot spots. In  
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12 339 light of the TI results, these areas of presumed atelectasis may actually represent  
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14 340 pneumonia. These opacities on CXR were, in one case each, in the right upper lobe,  
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16 341 left upper lobe and left lower lobe.  
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20 343 Three of the 11 false positive TI cases had no change in CXR interpretation.  
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24 345 The one false negative case had no change to TI or CXR interpretation.  
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28 347 There were no tumors, pulmonary edema or other abnormalities identified on CXR  
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30 348 that might affect TI results.  
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34 350 Non-blinded review produced no changes in interpretation of TI images.  
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38 352 Discussion  
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43 354 This study suggests that TI is sensitive and reasonably specific compared to the  
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45 355 outcome parameter of CXR in detecting focal pneumonia.  
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49 357 There currently is no experimental data assessing the mechanism of increased focal  
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51 358 heat, as detected by TI, associated with focal pneumonia. The assumption is that  
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53 359 the focal hyperemia associated with focal inflammation, in this case pneumonia,  
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55 360 produces focally increased heat. It presumably is this increased heat radiating from  
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57 361 the site of pneumonia that is detected by TI. Consequently, an area of atelectasis  
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3 362 which is not associated with hyperemia, will not produce an area of focally increased  
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5 363 heat.  
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9 365 It is focal increased heat that is the indicator of focal pneumonia on TI. Thus any  
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11 366 bacterial organism (which organism cannot be determined) may be the culprit. Viral  
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13 367 pneumonias are generally diffuse and do not typically generate a focal pneumonia.  
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15 368 Some atypical pneumonias, such as mycoplasma, may have a focal consolidative  
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17 369 component which might be detected as a hot spot. It has been reported in a case  
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19 370 report that acute consolidative tuberculosis caused a TI hot spot but sub-acute  
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21 371 tuberculosis did not (21). It is not the precise lobar distribution but rather presence  
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23 372 or absence of a focal hot spot that is the informative aspect of TI.  
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28 374 The purpose of this study is not to determine whether TI or CXR is superior in  
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30 375 detecting pneumonia but to assess how well TI and CXR agree in detecting a focal  
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32 376 consolidation. This is in the context of CXR being the most widely utilized standard  
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34 377 for diagnosis of pneumonia (19, 20, 24-29), including studies assessing effectiveness  
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36 378 of the WHO clinical diagnostic criteria (29). Ultrasound is the only other point of care  
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38 379 imaging procedure widely studied for diagnosis of pneumonia and in virtually all of its  
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40 380 validation studies it is compared to CXR (26-28). While clinical signs and symptoms  
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42 381 have been utilized, collecting accurate data and correlation with the ultimate  
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44 382 diagnosis of pneumonia is inconsistent (30). However, it is not the purpose of this  
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46 383 study to assess the accuracy of imaging to detect pneumonia as compared to the  
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48 384 clinical diagnosis. Ultimately, other methodologies such as inflammatory markers  
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50 385 may play a role, but currently these are in relatively early stages of development.  
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55 387 Accuracy of CXR in determining the presence of focal pneumonia will vary depending  
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57 388 on quality of imaging and experience of the observer, as is true for TI. Although  
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3 389 computerized tomography (CT) has greater accuracy in detecting pneumonia than  
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5 390 CXR (31-32), CT cannot be used as routine imaging for pneumonia because of  
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7 391 concerns of radiation exposure and cost (29).  
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10 392  
11 393 There was only one false negative in the cohort of 31 patients with 11 false positives  
12 394 (sensitivity = 0.80, specificity = 0.58). Thus the ability of TI to accurately detect  
13 395 focal pneumonia (as determined by CXR), in this cohort was high. For a screening  
14 396 test, this ability to not miss focal pneumonia is the most critical criterion. The higher  
15 397 rate of false positives would lead to either over treating or further testing in a limited  
16 398 number of patients, which, although important, is a less critical issue.

17 399 The changes in CXR interpretation on non-blinded review of discrepant TI/CXR  
18 400 revealed the following. 1) TI had hot spots in cases where CXR findings were initially  
19 401 not definitive for focal pneumonia (N = 5). For two, CXR diagnosis was confounded  
20 402 by pre-existing chronic lung diseases and in one by shallow inflation. For two others,  
21 403 the suggestion of focal pneumonia on CXR was too subtle for definitive diagnosis. 2)  
22 404 TI revealed hot spots in cases where the blinded CXR suggested atelectasis (N = 3).  
23 405 This suggests that TI may be able to detect focal pneumonia in cases where pre-  
24 406 existing lung disease or imaging technique confound the diagnosis on CXR or when  
25 407 diagnosis on CXR is too subtle to be convincing (as possibly with early onset or  
26 408 resolving focal pneumonia). TI may be able to differentiate between focal  
27 409 pneumonia and atelectasis.  
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49 411 These findings suggest TI may be comparable to CXR in recognizing focal  
50 412 pneumonia. Relatively low cost and portability of thermal cameras, some of which  
51 413 can be used with mobile phones, potentially enable TI as a point of care screening  
52 414 tool for focal pneumonia. Other advantages include minimal training to perform  
53 415 images, lack of ionizing radiation exposure, off-site interpretation of digitized images  
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3 416 and possible software interpretation algorithms. Lack of physical contact with the  
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5 417 patient enhances infection control. Possible additional uses include following  
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7 418 progression of disease in combination with other modalities such as respiratory rate  
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9 419 and oximetry.  
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13 421 Limitations of TI include learning to interpret TI, presence of prior disease affecting  
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15 422 TI and the possibility that increased adiposity may interfere with its accuracy.  
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20 424 Conclusions  
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24 426 This feasibility study confirms proof of concept that TI can demonstrate focal  
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26 427 pneumonia. Therefore, these findings support further investigation with larger trials  
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28 428 of patients that will be adequately powered to robustly assess the similarity between  
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30 429 TI and the outcome parameter. This technology is potentially most useful in  
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32 430 resource-limited environments where pneumonia is the second most common cause  
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34 431 of death in young children and where CXR equipment and expert readers are  
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36 432 unavailable (33). It also could be of benefit in high throughput healthcare settings,  
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38 433 such as emergency departments or busy doctors' offices and rural areas where  
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40 434 access to CXR is limited.  
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19 443 **Contributor ship Statement:**

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23 445 Specific Contributions from each author

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31 449 interpretation of data, and drafting the work and revising it critically

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36 452 Conception and design of the study, data analysis, interpretation of data, and

37 453 drafting the work and revising it critically.

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45 487 Competing Interests

46  
47 488 None of the authors have conflicts of interest to report relating to this work

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625 Tables

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	True Positive	True Negative	False Positive	False Negative	Sensitivity (95% CI)	Specificity (95% CI)	Positive Predictive Value	Negative Predictive Value
TI vs blinded CXR (5 +ve, 26 -ve)	4	15	11	1	80.0% (29.9%, 98.9%)	57.7% (37.2%, 76.0%)	26.7% (8.9%, 55.2%)	93.8% (67.7%, 99.7%)

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630 Table 1: Sensitivity analysis of TI assuming the CXR as the outcome parameter.

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10 Figure 1: CXR shows an opacity in the right lung base consistent with pneumonia.  
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13 Figure 2: TI obtained shortly after the CXR (Figure 1). The image is taken from the  
14 patient's back so that the patient's right is on the viewer's right. There is an area of  
15 increased heat (white area) in the right lung base concordant with the CXR.  
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19 Figure 3: Same image as Figure 2 with the area of pneumonia (white area) encircled  
20 by an oval ring.  
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30 Figure 4: Portable CXR taken in the Emergency Department during assessment for  
31 acute pneumonia reveals low lung volumes and what was assumed to be resultant  
32 crowding of pulmonary parenchyma in both lung bases medially. The interpretation  
33 at that time was that there was no acute pneumonia.  
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40 Figure 5: This CXR was performed 5 days before the CXR in Figure 4. The lung  
41 volumes are comparably low, but the small opacity in the right infrahilar region on  
42 Figure 4 is not present. This indicates that there was a pneumonia in the right lung  
43 base on the CXR in Figure 4 rather than normal crowding of lung tissue.  
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50 Figure 6: Same image as figure 4 with the right infrahilar pneumonia indicated by  
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Figure 7: TI obtained shortly after the CXR shown in Figure 4. The image is taken from the patient's back so that the patient's right is on the viewer's right. There is an area of increased heat (white area) in the right lung base concordant with that seen in Figure 4.

Figure 8: Same image as Figure 7 with the area of pneumonia (white area) encircled by an oval ring.

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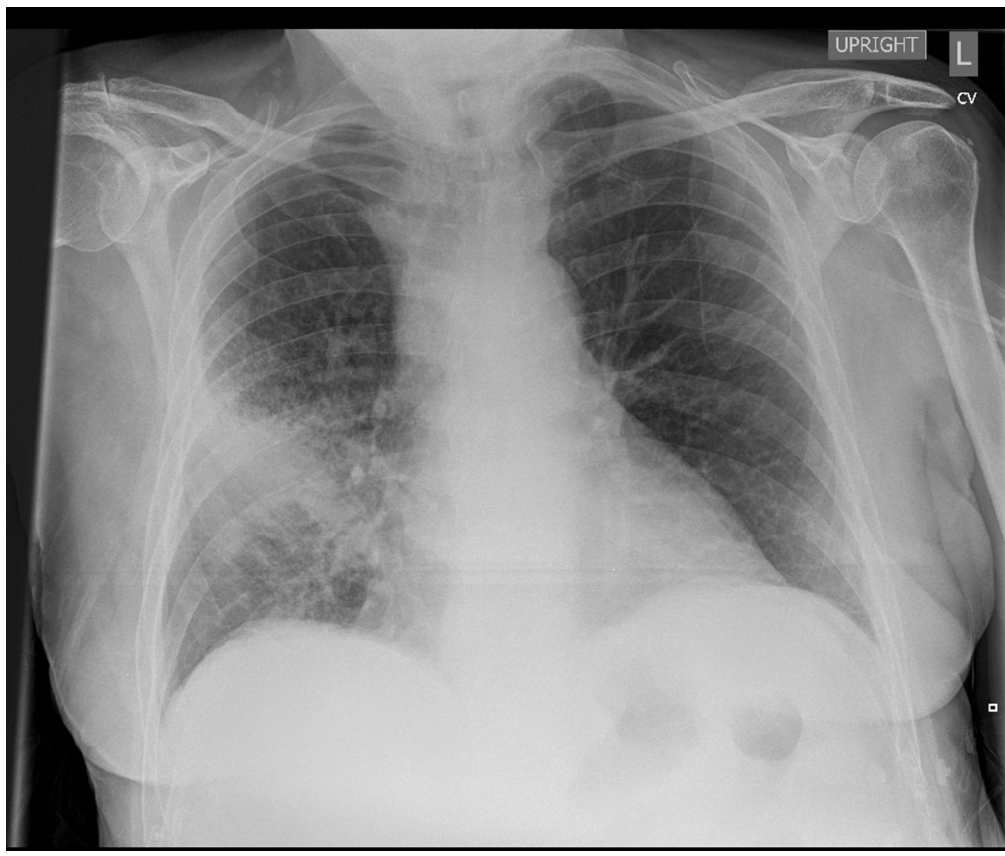


Figure 1: CXR shows an opacity in the right lung base consistent with pneumonia.

309x260mm (300 x 300 DPI)

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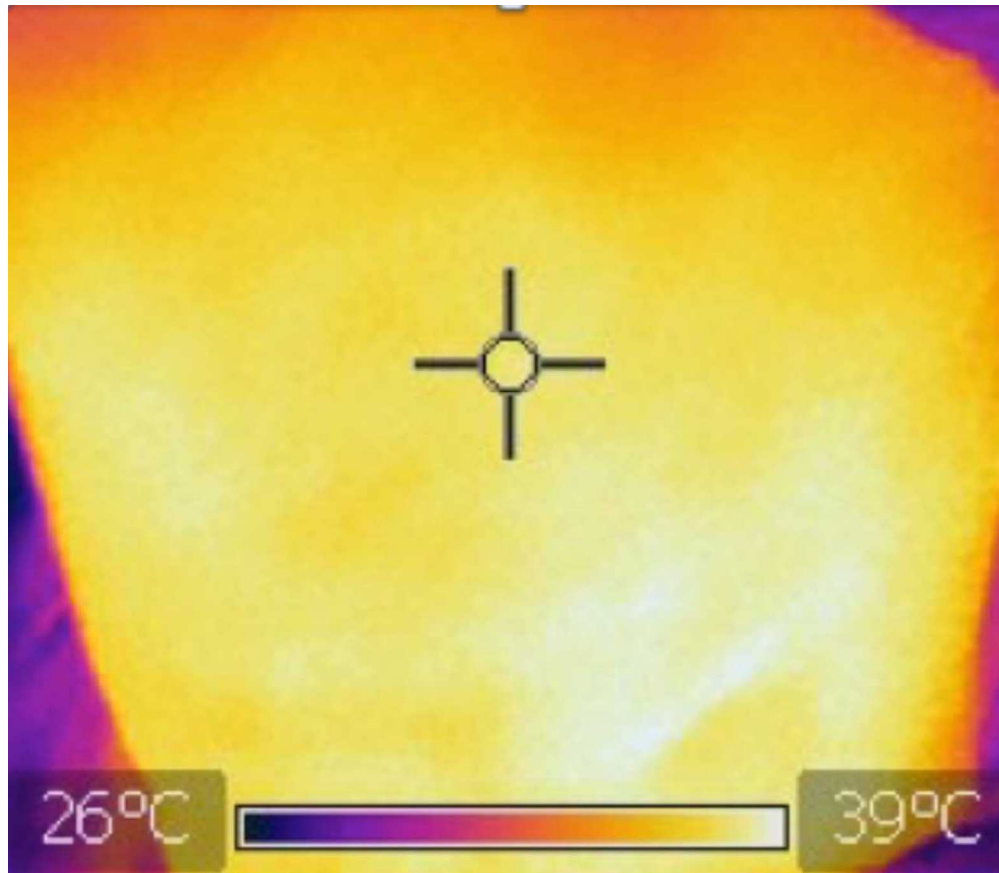


Figure 2: TI obtained shortly after the CXR (Figure 1). The image is taken from the patient's back so that the patient's right is on the viewer's right. There is an area of increased heat (white area) in the right lung base concordant with the CXR.

109x94mm (300 x 300 DPI)

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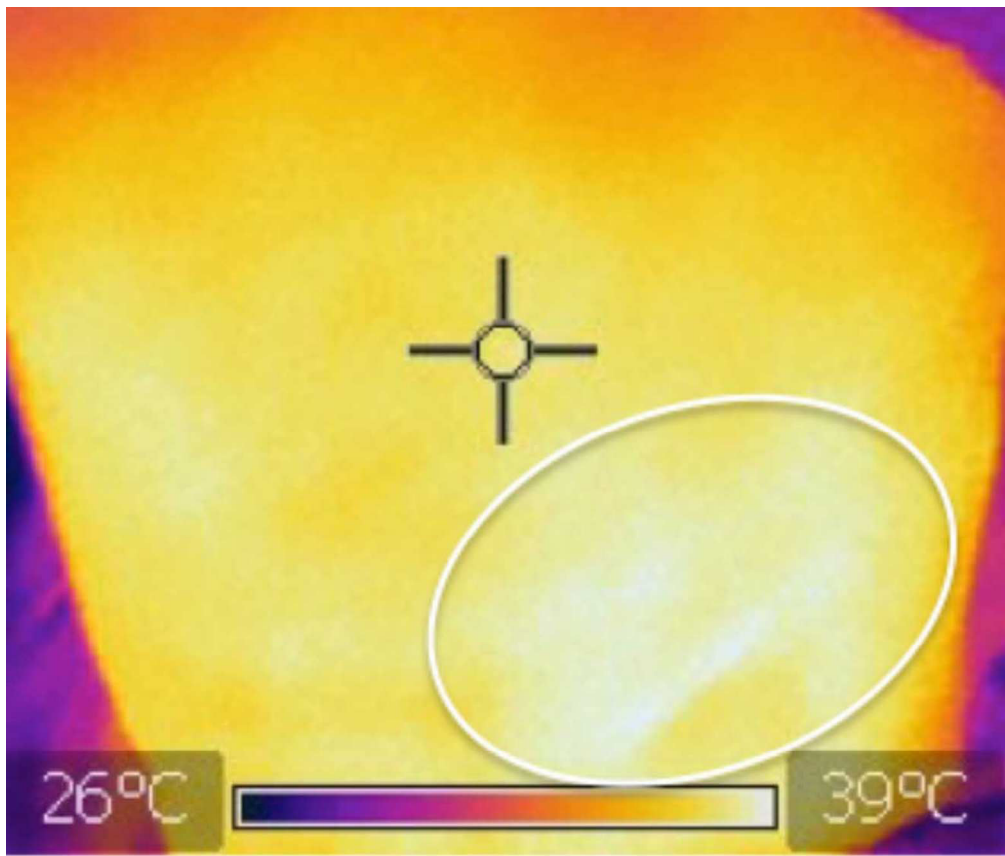


Figure 3: Same image as Figure 2 with the area of pneumonia (white area) encircled by an oval ring.

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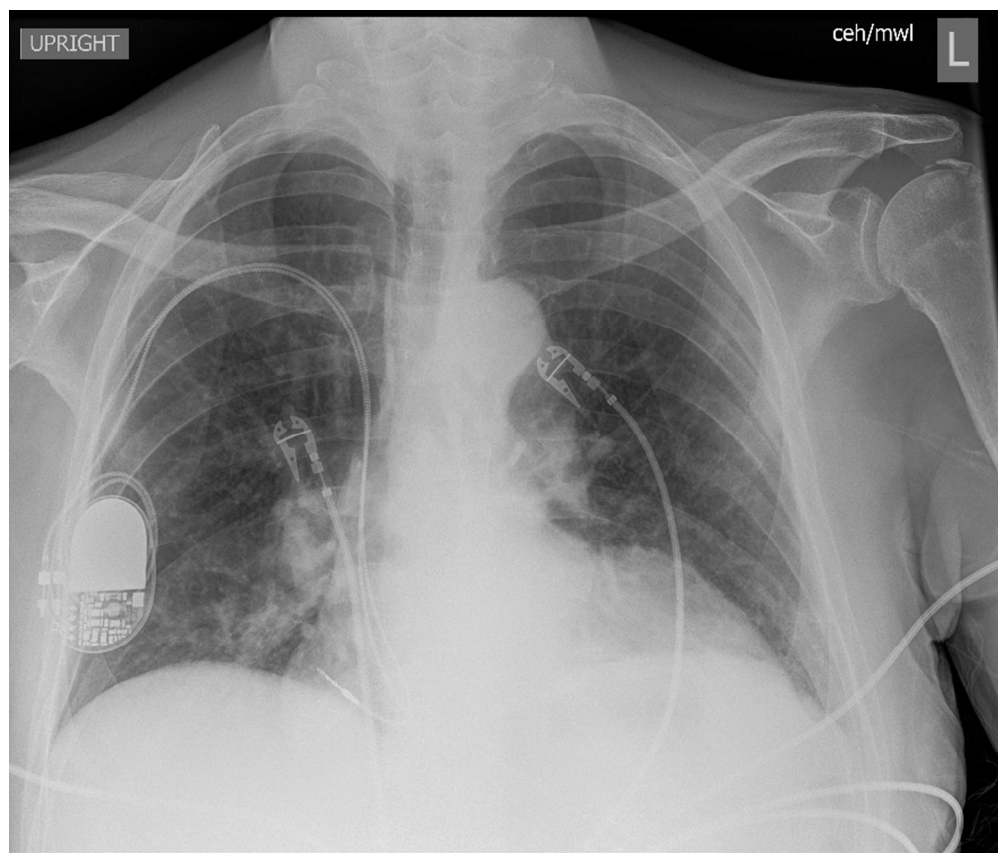


Figure 4: Portable CXR taken in the Emergency Department during assessment for acute pneumonia reveals low lung volumes and what was assumed to be resultant crowding of pulmonary parenchyma in both lung bases medially. The interpretation at that time was that there was no acute pneumonia.

311x264mm (300 x 300 DPI)

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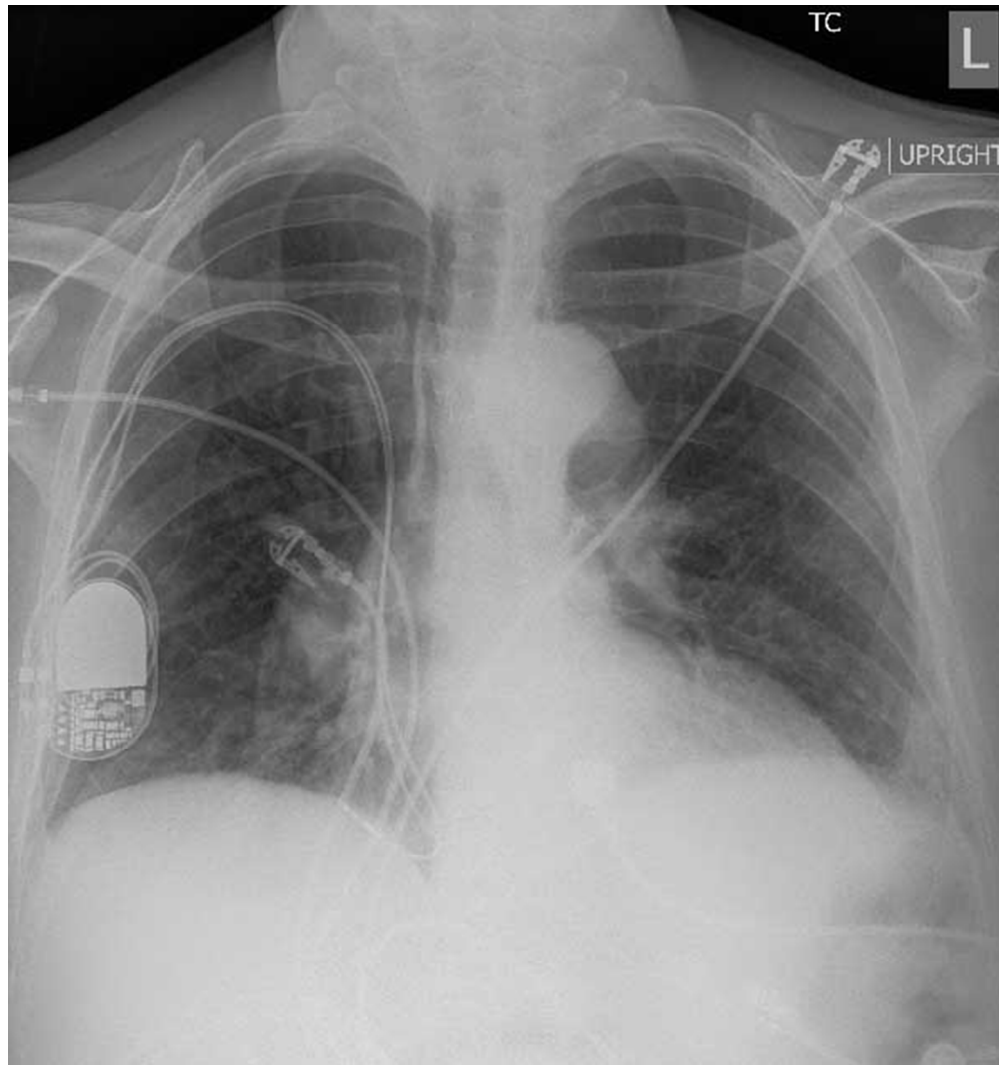


Figure 5: This CXR was performed 5 days before the CXR in Figure 4. The lung volumes are comparably low, but the small opacity in the right infrahilar region on Figure 4 is not present. This indicates that there was a pneumonia in the right lung base on the CXR in Figure 4 rather than normal crowding of lung tissue.

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Figure 6: Same image as figure 4 with the right infrahilar pneumonia indicated by arrows.

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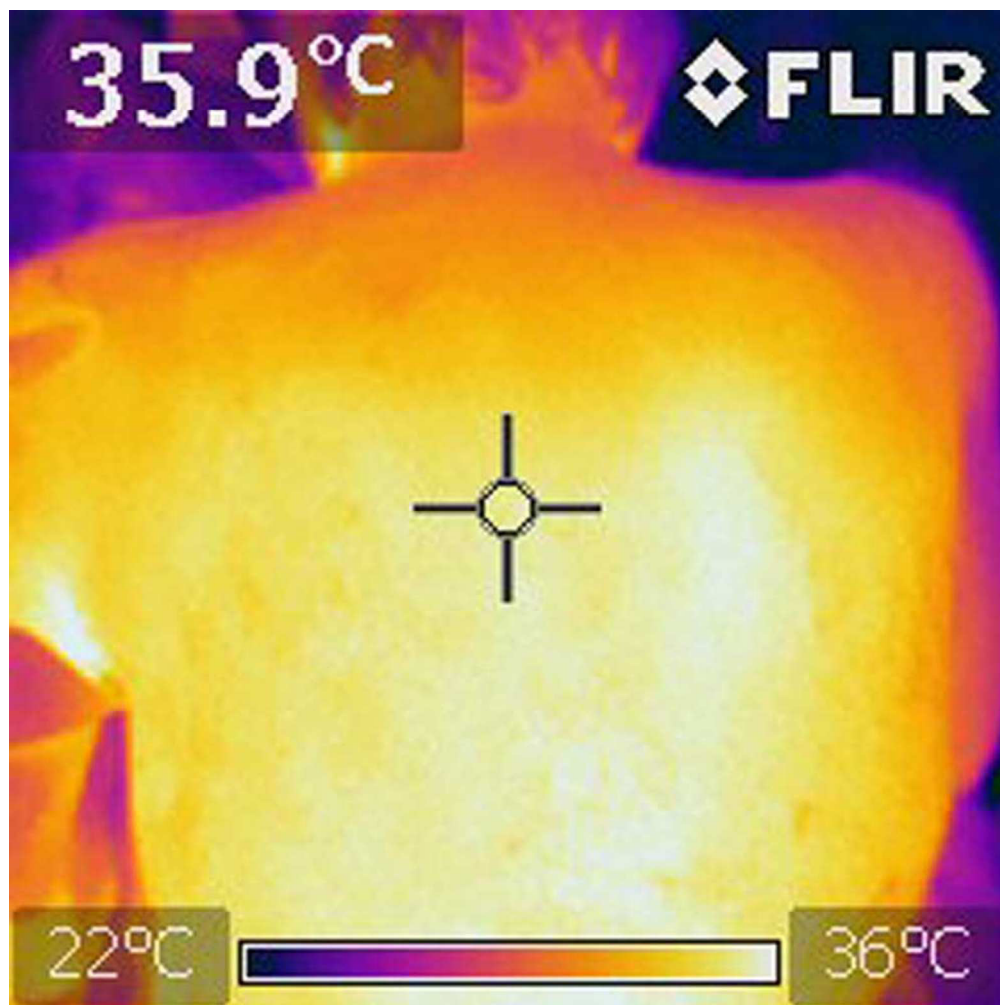


Figure 7: TI obtained shortly after the CXR shown in Figure 4. The image is taken from the patient's back so that the patient's right is on the viewer's right. There is an area of increased heat (white area) in the right lung base concordant with that seen in Figure 4.

84x84mm (300 x 300 DPI)

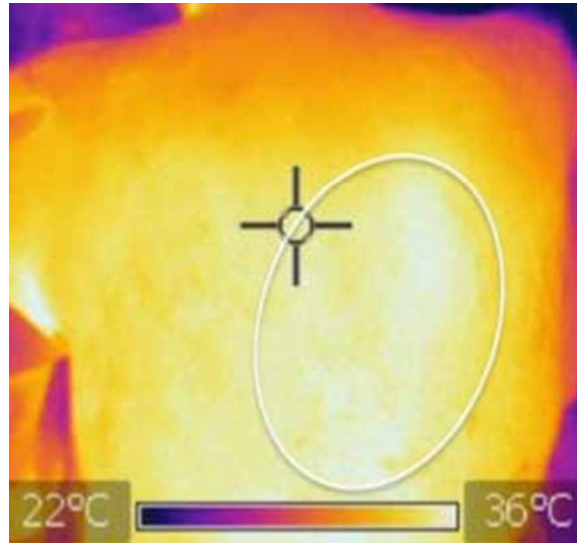


Figure 8: Same image as Figure 7 with the area of pneumonia (white area) encircled by an oval ring.

24x22mm (300 x 300 DPI)

review only

## Items to include when reporting a randomized trial in a journal or conference abstract

Item	Description	Reported on line number
Title	Identification of the study as randomized	1
Authors *	Contact details for the corresponding author	4 - 7
Trial design	Description of the trial design (e.g. parallel, cluster, non-inferiority)	132; 245
Methods		
Participants	Eligibility criteria for participants and the settings where the data were collected	139-153
Interventions	Interventions intended for each group	149-151, 168--188;
Objective	Specific objective or hypothesis	91-92; 126- 129; 257
Outcome	Clearly defined primary outcome for this report	185-189
Randomization	How participants were allocated to interventions	133; 149
Blinding (masking)	Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment	185-189
Results		
Numbers randomized	Number of participants randomized to each group	155
Recruitment	Trial status	
Numbers analysed	Number of participants analysed in each group	155-158
Outcome	For the primary outcome, a result for each group and the estimated effect size and its precision	258,291-297, 344
Harms	Important adverse events or side effects	
Conclusions	General interpretation of the results	427-435
Trial registration	Registration number and name of trial register	NA
Funding	Source of funding	Funding: The Bacca Foundation and the Consortium for Affordable Medical Technologies (CAMTech) (Fund # is 223707)

*\*this item is specific to conference abstracts*

# BMJ Open

## Similarity of Chest X-ray and Thermal Imaging of Focal Pneumonia: A Randomized Proof of Concept Study at a Large Urban Teaching Hospital

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-017964.R2
Article Type:	Research
Date Submitted by the Author:	17-Oct-2017
Complete List of Authors:	Wang, Linda; Massachusetts General Hospital, Emergency Medicine and Pediatric Global Health Cleveland, Robert; Children's Hospital Boston, Radiology Binder, William; Brown University, Emergency Medicine Zwerdling, Robert; university of massachusetts, radiology Stamoulis, Caterina; children's hospital of boston, adolescent and young adult research Ptak, Thomas; Emory University Hospital, Radiology Sherman, Mindy; Massachusetts General Hospital, Emergency Medicine Haver, Kenan; Children's Hospital Boston, Pulmonary and Respiratory Diseases Sagar, Pallavi; Massachusetts General Hospital, Radiology Hibberd, Patricia; Boston Medical Center, Department of Global Health
<b>Primary Subject Heading</b>:	Radiology and imaging
Secondary Subject Heading:	Global health, Respiratory medicine, Infectious diseases, Paediatrics
Keywords:	Paediatric radiology < PAEDIATRICS, Chest imaging < RADIOLOGY & IMAGING, Respiratory infections < THORACIC MEDICINE, Diagnostic radiology < RADIOLOGY & IMAGING

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Manuscripts

1 Similarity of Chest X-ray and Thermal Imaging of Focal Pneumonia: A randomized  
2 proof of concept study at a large urban teaching hospital.

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26 39 ABSTRACT  
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30 41 Objective: To assess the diagnostic accuracy of thermal imaging (TI) in the setting  
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32 42 of focal consolidative pneumonia with chest x-ray (CXR) as the gold standard.  
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36 44 Setting: A large, 973 bed teaching hospital in Boston, Massachusetts  
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40 46 Participants: 47 patients enrolled, 15 in a training set, 32 in a test set. Age range  
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42 47 10 months – 82 years (median = 50 years)  
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46 49 Materials and Methods: Subjects received CXR with subsequent TI within 4 hours of  
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48 50 each other. CXR and TI were assessed in blinded random order. Presence of focal  
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50 51 opacity (pneumonia) on CXR, the outcome parameter, was recorded. For TI,  
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52 52 presence of area(s) of increased heat (pneumonia) was recorded. Fisher's exact test  
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54 53 was used to assess the significance of the correlations of positive findings in the  
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56 54 same anatomic region.  
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56 Results: With TI compared to the CXR (the outcome parameter), sensitivity was  
57 80.0% (Confidence intervals (CI): [29.9%, 98.9%], specificity was 57.7% (CI:  
58 [37.2%, 76.0%]). Positive predictive value of TI was 26.7% (CI: [8.9%, 55.2%])  
59 and its negative predictive value was 93.8% (CI: [67.7%, 99.7%]).

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61 Conclusions: This feasibility study confirms proof of concept that chest TI is  
62 consistent with CXR in suggesting similarly localized focal pneumonia with high  
63 sensitivity and negative predictive value. Further investigation of TI as a point of  
64 care imaging modality is warranted.

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66 Strengths and Limitations:

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68 Strengths:

- 69 • Proof of concept suggesting that Thermal Imaging (TI) is a valid, innovative,  
70 and inexpensive technology useful for diagnosing bacterial pneumonia
- 71 • Proof of concept suggesting that Thermal Imaging (TI) is a rapid means of  
72 diagnosing focal pneumonia in high throughput settings
- 73 • Proof of concept suggesting that Thermal Imaging (TI) is a valid and  
74 innovative technology useful in diagnosing pneumonia in resource limited  
75 regions of the world

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77 Limitations:

- 78 • As this is a proof of concept study, it does not have adequate power to be  
79 definitive and cannot replace chest xray for detecting focal pneumonia

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4 80 • As this is a proof of concept study, limitations of the technology have not  
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6 81 been fully discerned, and at present include adipose tissue and interpretation,  
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8 82 but may include other concerns which will require higher numbers of patients  
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15 85• Data Sharing: There are no additional unpublished data from the study.  
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17 86 Data are available to any researcher who is interested in the data, and will be  
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19 87 able to be accessed through Dyad and/or through correspondence with the  
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21 88 contributing authors.  
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25 91 Introduction

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29 93 This study investigates the degree to which thermal imaging (TI) and chest x-ray  
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31 94 (CXR) are concordant in detecting similarly localized focal pneumonia. Often a  
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33 95 clinically challenging diagnosis, bacterial pneumonia remains a major cause of  
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35 96 morbidity and mortality worldwide, particularly in under-resourced environments (1-  
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37 97 3). Expert panels, including the World Health Organization (WHO), have formulated  
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39 98 algorithms to enhance clinical accuracy (4), typically focusing on aspects of the  
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41 99 medical history and physical examination to determine the likelihood of bacterial  
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43 100 pneumonia. Despite having these algorithms, CXR is generally performed to confirm  
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45 101 the diagnosis in severe infections (5-16). If TI results are similar to CXR, it might  
46  
47 102 substitute for CXR when CXR is not available. In resource-limited environments,  
48  
49 103 where 2/3 of the world's population has no access to diagnostic imaging (17-18), the  
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51 104 potential use of TI in point of care screening could aid decision making to treat for  
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53 105 pneumonia.  
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3 106 Point of care imaging utilizing ultrasonography to diagnose pneumonia is attracting  
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5 107 interest (19-20). However, ultrasonography requires costly equipment and specific  
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7 108 expertise for image acquisition and interpretation.  
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11 109  
12 110 Anecdotal reports suggest that TI has potential for detecting pneumonia (21-22).  
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14 111 These case reports and methodologies have not been subjected to systematic  
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16 112 blinded assessment. In this initial proof of concept investigation, we compared TI to  
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18 113 CXR in patients suspected of having acute pneumonia.  
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22 115 With recent advances in infrared technology and increasing use assessing home heat  
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24 116 loss, low-cost thermal cameras have become available, currently costing as little as  
25  
26 117 \$200-\$300 (Flir.com). Installation of shielded radiographic rooms can cost hundreds  
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28 118 of thousands of dollars. Portable x-ray units capable of performing CXR can cost as  
29  
30 119 little as \$600-\$800 (dotmed.com). If uninsured, patient cost of a CXR in the US is  
31  
32 120 \$200-\$400 or, if insured, a co-pay of \$10-\$50 (23).  
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36 122 For TI there are no additional costs beyond cost of the camera. TI cameras are  
37  
38 123 portable and operate with rechargeable batteries. TI is essentially identical to taking  
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40 124 a "snap and shoot" photograph and can be done in seconds during the primary  
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42 125 patient encounter without the camera physically contacting the patient. Digital  
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44 126 storage and transfer of TI is simple, utilizing a memory card in the TI device that can  
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46 127 be uploaded to a computer.  
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50 129 This study presents a prospective comparison of TI to CXR using a commercially  
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52 130 available thermal camera to determine the similarity of TI and CXR in the setting of  
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54 131 possible focal pneumonia and thus proof of concept and feasibility of TI to detect  
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56 132 focal pneumonia.  
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3 1334  
5 134 Materials and Methods6  
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9 136 Subjects: Participants came from the Emergency Department of Massachusetts  
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11 137 General Hospital (Boston, MA). On admission to the Emergency Department, adult  
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13 138 patients and families of children who had CXR included for evaluation of pneumonia  
14  
15 139 were approached to discuss study participation. Written informed consent and, when  
16  
17 140 applicable, participant assent was obtained from all participants. Enrollment  
18  
19 141 occurred Monday - Friday, 7:00am - 11:00pm when research staff was available.  
20  
21 142 Partners Human Research Committee approved the HIPPA compliant study protocol  
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23 143 (#2013P001247).  
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28 145 In an initial Training Set, subjects were excluded if they had chronic lung disease,  
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30 146 congestive heart failure, prior chest surgery or immunosuppression. In a subsequent  
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32 147 TEST Set, these exclusions were not used. Patients had TI within 4 hours of CXR.  
33  
34 148 Patients were male older than 28 days, or female older than 28 days and younger  
35  
36 149 than 8 years. After age eight, only males were included because of concerns for  
37  
38 150 modesty.  
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42 152 Forty-seven patients were enrolled. The first 15, comprising the Training Set, were  
43  
44 153 not included as a part of the study's statistical assessment. These 15 cases provided  
45  
46 154 a spectrum of results with 10 concordant for focal pneumonia, 2 concordant for no  
47  
48 155 focal pneumonia, and 3 discordant for pneumonia. The remaining 32 subjects  
49  
50 156 comprised the TEST Set. Analysis of the TEST Set included 31 patients (28 males, 3  
51  
52 157 females), one patient had no usable thermal images. Patient age ranged from 10  
53  
54 158 months - 82 years (median = 50.0 years, (25th, 75th) quartiles = (11.5, 60.5  
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56 159 years), with 8 subjects  $\leq$  18 years and 23 subjects  $>$  18 years.  
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5 161 Imaging and interpretation: The radiologist interpreting CXR and TI (RHC) is an6  
7 162 American Board of Radiology certified diagnostic radiologist and sub-certified8  
9 163 pediatric radiologist with 40 years experience.10  
11 16412  
13 165 CXRs were assessed in random order blinded to TI. If focal opacities were found, the14  
15 166 lobe(s) were recorded (figure 1a). The lobes involved were precisely determined16  
17 167 with posterior-anterior (PA) and lateral examinations. When only a portable18  
19 168 anterior-posterior (AP) image could be obtained, the lobe(s) involved was20  
21 169 determined by lung zone and presence/absence of silhouetting of the mediastinum.22  
23 170 CXRs were taken in PA and lateral projections (N = 19). If PA and lateral imaging24  
25 171 could not be performed, because of clinical care requirements, a portable AP image26  
27 172 was acquired (N = 12).28  
29 17330  
31 174 TI of the chest were taken from the neck down, similar to CXR, with both posterior32  
33 175 and anterior views whenever possible (N = 29). If a patient was too ill to be34  
35 176 positioned for two views only 1 view was obtained. Depending on the patients'36  
37 177 condition and preferred position, 1 patient had a posterior view and 1 an anterior38  
39 178 view. Oblique images were not obtained since TI interpretation depends on40  
41 179 assessment of asymmetric heat distribution. TI were acquired with the commercially42  
43 180 available FLIR i7 infrared thermal camera (flir.com). The subject was encompassed44  
45 181 in the field of view; a "snapshot" was obtained so the patient's chest filled the field of46  
47 182 view with the entire chest from side to side included from the level of the shoulders48  
49 183 to bottom of the chest (or below). Patient to camera distance varied based on patient50  
51 184 size. Subjects could be sitting or recumbent with the chest exposed. Clothing was52  
53 185 removed from the chest prior to TI acquisition.54  
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3 187 The camera used in this study has a resolution of 19,600 pixels detecting a  
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5 188 temperature range -4° Fahrenheit - 482° Fahrenheit (-20° Celsius - 250° Celsius)  
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7 189 with sensitivity to 0.1 degree Celsius. Images filled the 2.8 inch LCD TI screen. TI  
8  
9 190 were interpreted while displayed on a desk top computer at a size comparable to the  
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11 191 size of the CXR, filling roughly 50% of the computer monitor screen. TI image size  
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13 192 varies depending on the imaging device. TI stored in the camera's memory can be  
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15 193 uploaded to a computer and displayed at whatever size preferred.  
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19 195 TI were evaluated in random order blinded to CXR. Any area(s) of increased heat  
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21 196 were recorded as upper, mid or lower lung zone, and identified as in the right or left  
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23 197 lung. (figures 1,2,3). Following initial assessment of blinded TI and CXR, to shed  
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25 198 light on possible causes for TI/CXR discrepancies, cases with disagreement were  
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27 199 reviewed in non-blinded fashion, using prior CXR when available.  
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35 205 (INSERT FIGURES 1, 2, 3)  
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46 206 Legend

47 207 Figure 1: CXR shows an opacity in the right lung base consistent with pneumonia.  
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49 209 Figure 2: TI obtained shortly after the CXR (Figure 1). The image is taken from the  
50 210 patient's back so that the patient's right is on the viewer's right. There is an area of  
51 211 increased heat (white area) in the right lung base concordant with the CXR.  
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3 213 Figure 3: Same image as Figure 2 with the area of pneumonia (white area) encircled  
4 by an oval ring.  
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222 TI is similar to nuclear medicine imaging in that it is not the precise size,  
223 configuration or margins that are of importance, but rather the temperature pattern  
224 with presence or absence of focal areas of increased heat, "hot spots," that is  
225 informative for focal pneumonia. Heat emanating from the patient's skin determines  
226 the TI image. Generalized skin temperature does not affect TI recognition of a hot  
227 spot. Since clothing recently removed from the chest might affect skin temperature  
228 globally but not focally, it is unlikely that previously removed clothing would affect  
229 recognition of a hot spot. Areas of symmetric increased heat were considered to  
230 represent normal variation in heat pattern and areas of increased heat over the  
231 neck, sternum, supraclavicular space, spine and axillae were determined to be  
232 normal on the initial 15 training cases. Abdominal heat pattern is similar to that of  
233 the chest without focal temperature changes relating to abdominal viscera. Unlike  
234 CXR, TI does not require that patients hold their breath. Therefore, minor patient  
235 motion will have minor, if any, effect on TI quality.

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237 Statistical Methods: Paired data were constructed for each patient with CXR the  
238 standard for disease and TI the test variable. Each image was dichotomized as  
239 normal or showing focal pneumonia. TI sensitivity, specificity, positive predictive

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3 240 value and negative predictive value and their respective confidence intervals were  
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5 241 estimated. Agreement between CXR and TI (modeled as a binary outcome with  
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7 242 agreement = 1 and disagreement = 0) and as a function of patient age and sex was  
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9 243 assessed using simple logistic regression models, as well as 2X2 contingency tables  
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11 244 with age dichotomized as >18 years for adults and  $\leq$  18 years for children. Fisher's  
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13 245 exact test was used to assess significance of correlation between age (or sex) and  
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15 246 similarity between CXR and TI. Finally, despite the small sample, Cohen's kappa was  
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17 247 also used as an imperfect measure of agreement between the two modalities (24,  
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19 248 25). A significance level of 0.05 was assumed.  
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## 24 250 Results

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26 251  
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28 252 This study assessed the diagnostic sensitivity and specificity of TI using the chest  
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30 253 CXR as the gold standard. . For the overall cohort, five patients were identified as  
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32 254 having focal pneumonia by CXR and 26 not. For the pediatric cohort, there were 2  
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34 255 with focal pneumonia, 6 without by CXR.  
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39 257 Eleven cases were TI positive and CXR negative (false positives). One case was TI  
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41 258 negative and CXR positive (false negative).  
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45 260 Table 1 summarizes the TI sensitivity, specificity, positive predictive value, negative  
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47 261 predictive values and their corresponding confidence intervals (CI). .  
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	True Positive	True Negative	False Positive	False Negative	Sensitivity (95% CI)	Specificity (95% CI)	Positive Predictive Value	Negative Predictive Value
TI vs unblinded CXR (3 positive, 2 negative)	4	15	11	1	80.0% (29.9%, 98.9%)	57.7% (37.2%, 76.0%)	26.7% (8.9%, 55.2%)	93.8% (67.7%, 99.7%)

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263 Table 1: Sensitivity analysis of TI assuming the CXR as the gold standard. 95%

264 Confidence intervals (CI) are included for all parameters.

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267 The relationship between TI and CXR agreement with patient demographics was  
 268 assessed using logistic regression models and simple contingency tables. There was  
 269 no significant association between modality agreement and patient age (treated as a  
 270 continuous variable or dichotomized as adult versus pediatric) or sex (age:  $p = 0.3$   
 271 (95% CI for the regression coefficient = (-0.01, 0.004), odds ratio (OR) = 0.99, CI =  
 272 (0.99, 1.00)]; sex:  $p = 0.16$  [95% CI = (-0.16, 1.05), OR = 1.53, CI = (0.85,  
 273 2.85)]. Similar results were obtained when individual contingency tables for sex ( $p =$   
 274 0.54) or dichotomized age (>18 versus  $\leq 18$  years;  $p = 0.53$ ) were used. Despite its  
 275 limitations in small samples (24, 25), Cohen's kappa was also estimated as an  
 276 imperfect measure of agreement between TI and CXR [kappa = 0.21, CI = (-0.1421,  
 277 0.5591)]. Even when CXRs were unblinded, kappa = 0.48 [CI = (0.16, 0.79)]. The  
 278 wide confidence intervals are a further indication of the limitations of kappa to  
 279 quantify agreement in small samples.

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Since this is an exploratory proof of concept study the sample size is not based on statistical power. In order to achieve a power of 0.80, with the conditions encountered in this study, a power calculation showed 138 patients would be required. Furthermore, the sample size required to detect even modest agreement quantified by kappa is  $n \geq 40$  patients.

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To investigate causes for TI/CXR discrepancies, cases with disagreement were reviewed in a non-blinded fashion, using prior and subsequent CXR (comparison images were not included in the blinded, original CXR assessments). This review of discrepant cases is not included in the study's statistical analysis.

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For the 11 false positive TI cases, prior CXRs were available in only three cases. Each of these 3 cases had diffuse findings confounding CXR interpretation. One had diffuse changes of cystic fibrosis, one had changes of chronic obstructive pulmonary disease and one had low lung volumes. When CXR was reviewed with prior CXR, the CXR interpretation was changed to focal pneumonia (figure 4,5,6) concordant with TI (figure 7,8) in each instance. Follow-up images provided no additional information.

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(INSERT FIGURES 4, 5, 6, 7, 8)

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Legend



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3 306 Figure 4: Portable CXR taken in the Emergency Department during assessment for  
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5 307 acute pneumonia reveals low lung volumes and what was assumed to be resultant  
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7 308 crowding of pulmonary parenchyma in both lung bases medially. The interpretation  
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9 309 at that time was that there was no acute pneumonia.  
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14 311 Figure 5: This CXR was performed 5 days before the CXR in Figure 4. The lung  
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16 312 volumes are comparably low, but the small opacity in the right infrahilar region on  
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18 313 Figure 4 is not present. This indicates that there was a pneumonia in the right lung  
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20 314 base on the CXR in Figure 4 rather than normal crowding of lung tissue.  
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24 316 Figure 6: Same image as figure 4 with the right infrahilar pneumonia indicated by  
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26 317 arrows.  
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30 319 Figure 7: TI obtained shortly after the CXR shown in Figure 4. The image is taken  
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32 320 from the patient's back so that the patient's right is on the viewer's right. There is  
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34 321 an area of increased heat (white area) in the right lung base concordant with that  
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36 322 seen in Figure 4.  
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40 324 Figure 8: Same image as Figure 7 with the area of pneumonia (white area) encircled  
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42 325 by an oval ring.  
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49 328 For 2 other cases, knowledge of TI findings resulted in a change in the CXR  
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51 329 interpretation. For one case, the CXR interpretation was changed to a faint opacity,  
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53 330 consistent with focal pneumonia and in one case, there was the question of a very  
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55 331 subtle opacity, both concordant with the TI images.  
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3 333 Three other CXRs had what appeared to be atelectasis in regions of TI hot spots. In  
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5 334 light of the TI results, these areas of presumed atelectasis may actually represent  
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7 335 pneumonia. These opacities on CXR were, in one case each, in the right upper lobe,  
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9 336 left upper lobe and left lower lobe.  
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14 338 Three of the 11 false positive TI cases had no change in CXR interpretation.

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18 340 The one false negative case had no change to TI or CXR interpretation.

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22 342 There were no tumors, pulmonary edema or other abnormalities identified on CXR  
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24 343 that might affect TI results.  
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28 345 Non-blinded review produced no changes in interpretation of TI images.  
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32 347 Discussion  
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37 349 This study suggests that TI is sensitive and modestly specific compared to CXR in  
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39 350 detecting focal pneumonia.  
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43 352 There currently is no experimental data assessing the mechanism of increased focal  
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45 353 heat, as detected by TI, associated with focal pneumonia. The assumption is that  
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47 354 the focal hyperemia associated with focal inflammation, in this case pneumonia,  
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49 355 produces focally increased heat. It presumably is this increased heat radiating from  
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51 356 the site of pneumonia that is detected by TI. Consequently, an area of atelectasis  
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53 357 which is not associated with hyperemia, will not produce an area of focally increased  
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55 358 heat.  
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3 360 It is focal increased heat that is the indicator of focal pneumonia on TI. Thus any  
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5 361 bacterial organism (which organism cannot be determined) may be the culprit. Viral  
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7 362 pneumonias are generally diffuse and do not typically generate a focal pneumonia.  
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10 363 Some atypical pneumonias, such as mycoplasma, may have a focal consolidative  
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12 364 component which might be detected as a hot spot. It has been reported in a case  
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14 365 report that acute consolidative tuberculosis caused a TI hot spot but sub-acute  
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16 366 tuberculosis did not (21). It is not the precise lobar distribution but rather presence  
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18 367 or absence of a focal hot spot that is the informative aspect of TI.  
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20 368  
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22 369 The purpose of this study was to assess the sensitivity and specificity of TI , in  
23  
24 370 detecting a focal consolidation, using CXR as the gold standard given its wide use  
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26 371 for diagnosis of pneumonia (19, 20, 26-31), including studies assessing effectiveness  
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28 372 of the WHO clinical diagnostic criteria (31). Ultrasound is the only other point of care  
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30 373 imaging procedure widely studied for diagnosis of pneumonia and in virtually all of its  
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32 374 validation studies it is compared to CXR (28-30). While clinical signs and symptoms  
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34 375 have been utilized, collecting accurate data and correlation with the ultimate  
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36 376 diagnosis of pneumonia is inconsistent (32). However, it is not the purpose of this  
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38 377 study to assess the accuracy of imaging to detect pneumonia as compared to the  
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40 378 clinical diagnosis. Ultimately, other methodologies such as inflammatory markers  
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42 379 may play a role, but currently these are in relatively early stages of development.  
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47 381 Accuracy of CXR in determining the presence of focal pneumonia will vary depending  
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49 382 on quality of imaging and experience of the observer, as is true for TI. Although  
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51 383 computerized tomography (CT) has greater accuracy in detecting pneumonia than  
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53 384 CXR (33-34), CT cannot be used as routine imaging for pneumonia because of  
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55 385 concerns of radiation exposure and cost (31).  
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3 387 There was only one false negative in the cohort of 31 patients with 11 false positives  
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5 388 (sensitivity = 0.80, specificity = 0.58). Thus the ability of TI to accurately detect  
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7 389 focal pneumonia (as determined by CXR), in this cohort was relatively high. For a  
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9 390 screening test, this ability to not miss focal pneumonia is the most critical criterion.  
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11 391 The higher rate of false positives would lead to either over-treating or further testing  
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13 392 in a limited number of patients, which, although important, is a less critical issue.  
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15 393 The changes in CXR interpretation on non-blinded review of discrepant TI/CXR  
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17 394 revealed the following. 1) TI had hot spots in cases where CXR findings were initially  
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19 395 not definitive for focal pneumonia (N = 5). For two, CXR diagnosis was confounded  
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21 396 by pre-existing chronic lung diseases and in one by shallow inflation. For two others,  
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23 397 the suggestion of focal pneumonia on CXR was too subtle for definitive diagnosis. 2)  
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25 398 TI revealed hot spots in cases where the blinded CXR suggested atelectasis (N = 3).  
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27 399 This suggests that TI may be able to detect focal pneumonia in cases where pre-  
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29 400 existing lung disease or imaging technique confound the diagnosis on CXR or when  
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31 401 diagnosis on CXR is too subtle to be convincing (as possibly with early onset or  
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33 402 resolving focal pneumonia). TI may be able to differentiate between focal  
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35 403 pneumonia and atelectasis.  
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39 405 These findings suggest TI may be comparable to CXR in recognizing focal  
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41 406 pneumonia. Relatively low cost and portability of thermal cameras, some of which  
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43 407 can be used with mobile phones, potentially enable TI as a point of care screening  
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45 408 tool for focal pneumonia. Other advantages include minimal training to perform  
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47 409 images, lack of ionizing radiation exposure, off-site interpretation of digitized images  
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49 410 and possible software interpretation algorithms. Lack of physical contact with the  
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51 411 patient enhances infection control. Possible additional uses include following  
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53 412 progression of disease in combination with other modalities such as respiratory rate  
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55 413 and oximetry.  
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5 415 Limitations of TI include learning to interpret TI, presence of prior disease affecting  
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7 416 TI and the possibility that increased adiposity may interfere with its accuracy.  
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11 418 Conclusions

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15 420 This feasibility study confirms proof of concept that TI can demonstrate focal  
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17 421 pneumonia. Therefore, these findings support further investigation with larger trials  
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19 422 of patients that will be adequately powered to robustly assess the similarity between  
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21 423 TI and the outcome parameter. This technology is potentially most useful in  
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23 424 resource-limited environments where pneumonia is the second most common cause  
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25 425 of death in young children and where CXR equipment and expert readers are  
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27 426 unavailable (35). It also could be of benefit in high throughput healthcare settings,  
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29 427 such as emergency departments or busy doctors' offices and rural areas where  
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31 428 access to CXR is limited.  
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13 435 2016.

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19 437 **Contributor ship Statement:**

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22  
23 439 Specific Contributions from each author

24  
25  
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27  
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30 442 Conception and design of the study, acquisition of data and analysis,

31  
32 443 interpretation of data, and drafting the work and revising it critically

33  
34 444

35 445 Robert H. Cleveland, MD

36 446 Conception and design of the study, data analysis, interpretation of data, and  
37 447 drafting the work and revising it critically.

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42 451 drafting the work and revising it critically

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9 463 Kenan Haver, MD  
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11 464 Conception and design of the study, analysis of the data, interpretation of data,  
12 465 and drafting the work and revising it critically.  
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28 472 Conception and design of the study, data analysis, interpretation of data, and  
29 473 drafting the work and revising it critically.  
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33 475 Patricia Hibberd, MD, PhD  
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35 476 Conception and design of the study, interpretation of data, and drafting the work  
36 477 and revising it critically  
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45 481 Competing Interests  
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47 482 None of the authors have conflicts of interest to report relating to this work  
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51 483 "All authors have completed the ICMJE uniform disclosure form at [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and  
52 484 declare: no support from any organisation for the submitted work; no financial relationships with any  
53 485 organisations that might have an interest in the submitted work in the previous three years; no other  
54 486 relationships or activities that could appear to have influenced the submitted work."  
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626 Tables

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628

	True Positive	True Negative	False Positive	False Negative	Sensitivity (95% CI)	Specificity (95% CI)	Positive Predictive Value	Negative Predictive Value
TI vs blinded CXR (5 positive, 26 negative)	4	15	11	1	80.0% (29.9%, 98.9%)	57.7% (37.2%, 76.0%)	26.7% (8.9%, 55.2%)	93.8% (67.7%, 99.9%)

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631 Table 1: Sensitivity analysis of TI assuming the CXR as the outcome parameter.

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10 640 Figure 1: CXR shows an opacity in the right lung base consistent with pneumonia.  
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14 642 Figure 2: TI obtained shortly after the CXR (Figure 1). The image is taken from the  
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16 643 patient's back so that the patient's right is on the viewer's right. There is an area of  
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18 644 increased heat (white area) in the right lung base concordant with the CXR.  
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22 646 Figure 3: Same image as Figure 2 with the area of pneumonia (white area) encircled  
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24 647 by an oval ring.  
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30 650 Figure 4: Portable CXR taken in the Emergency Department during assessment for  
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32 651 acute pneumonia reveals low lung volumes and what was assumed to be resultant  
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34 652 crowding of pulmonary parenchyma in both lung bases medially. The interpretation  
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36 653 at that time was that there was no acute pneumonia.  
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40 655 Figure 5: This CXR was performed 5 days before the CXR in Figure 4. The lung  
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42 656 volumes are comparably low, but the small opacity in the right infrahilar region on  
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44 657 Figure 4 is not present. This indicates that there was a pneumonia in the right lung  
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46 658 base on the CXR in Figure 4 rather than normal crowding of lung tissue.  
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51 660 Figure 6: Same image as figure 4 with the right infrahilar pneumonia indicated by  
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53 661 arrows.  
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3 663 Figure 7: TI obtained shortly after the CXR shown in Figure 4. The image is taken  
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5 664 from the patient's back so that the patient's right is on the viewer's right. There is  
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7 665 an area of increased heat (white area) in the right lung base concordant with that  
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9 666 seen in Figure 4.  
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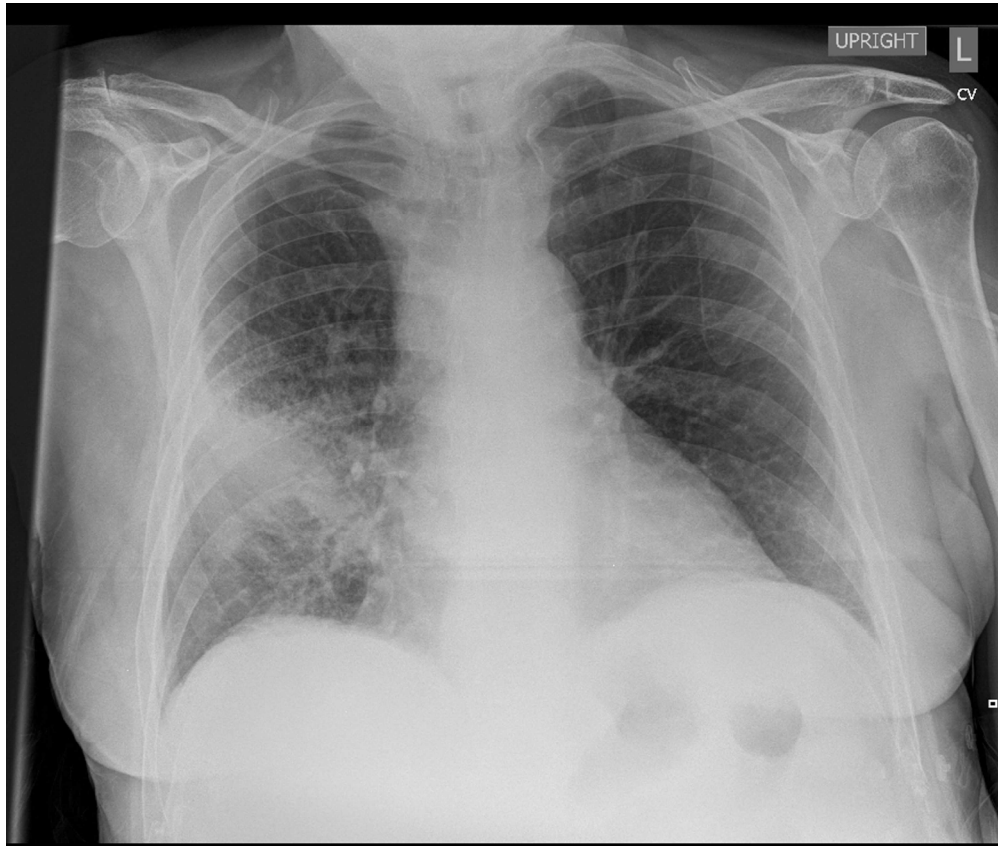


Figure 1: CXR shows an opacity in the right lung base consistent with pneumonia.

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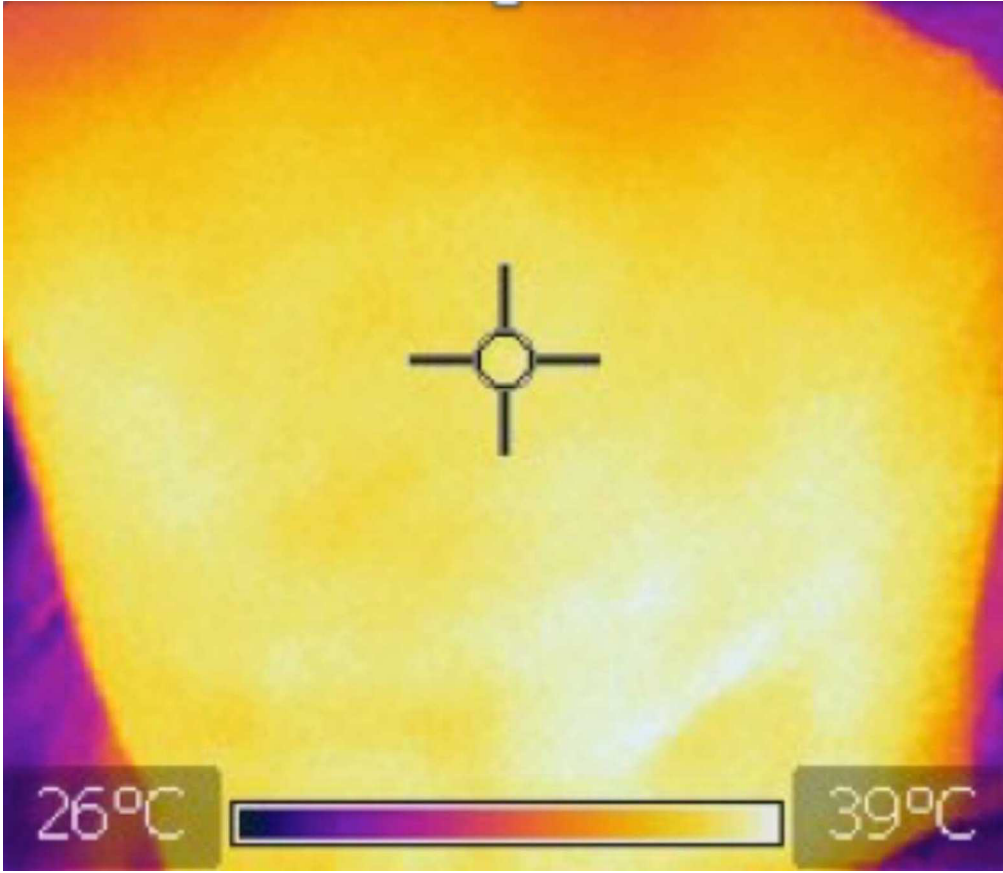


Figure 2: TI obtained shortly after the CXR (Figure 1). The image is taken from the patient's back so that the patient's right is on the viewer's right. There is an area of increased heat (white area) in the right lung base concordant with the CXR.

109x94mm (300 x 300 DPI)

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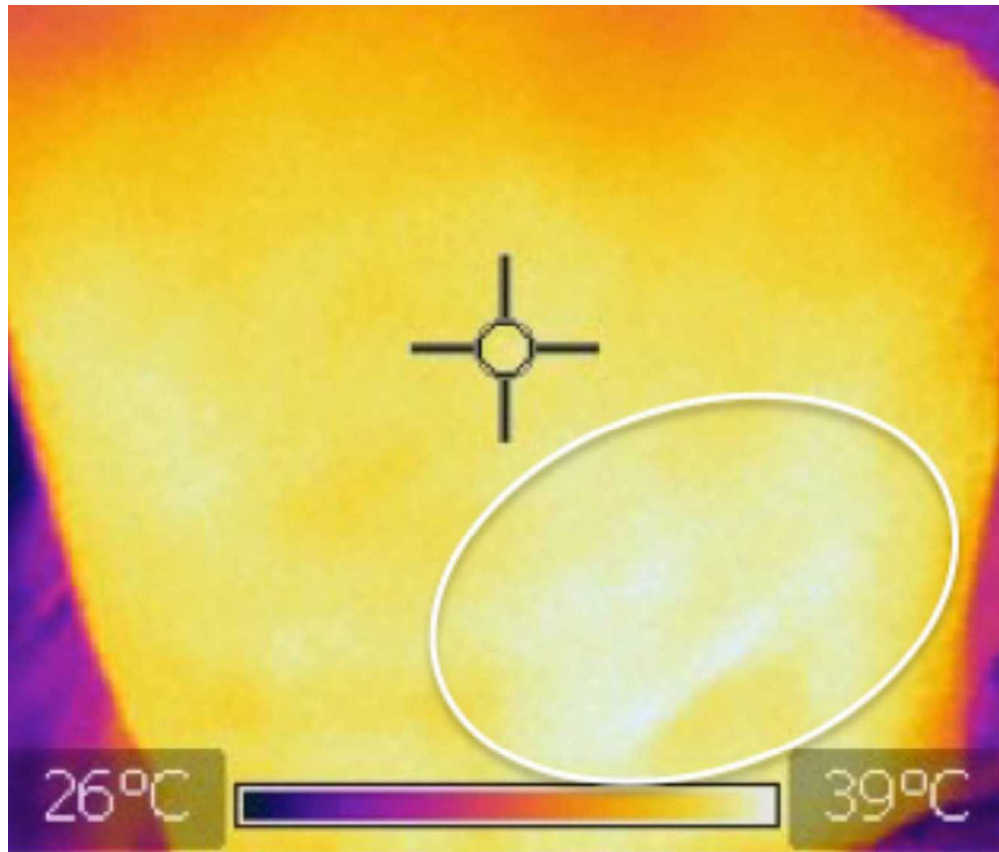


Figure 3: Same image as Figure 2 with the area of pneumonia (white area) encircled by an oval ring.

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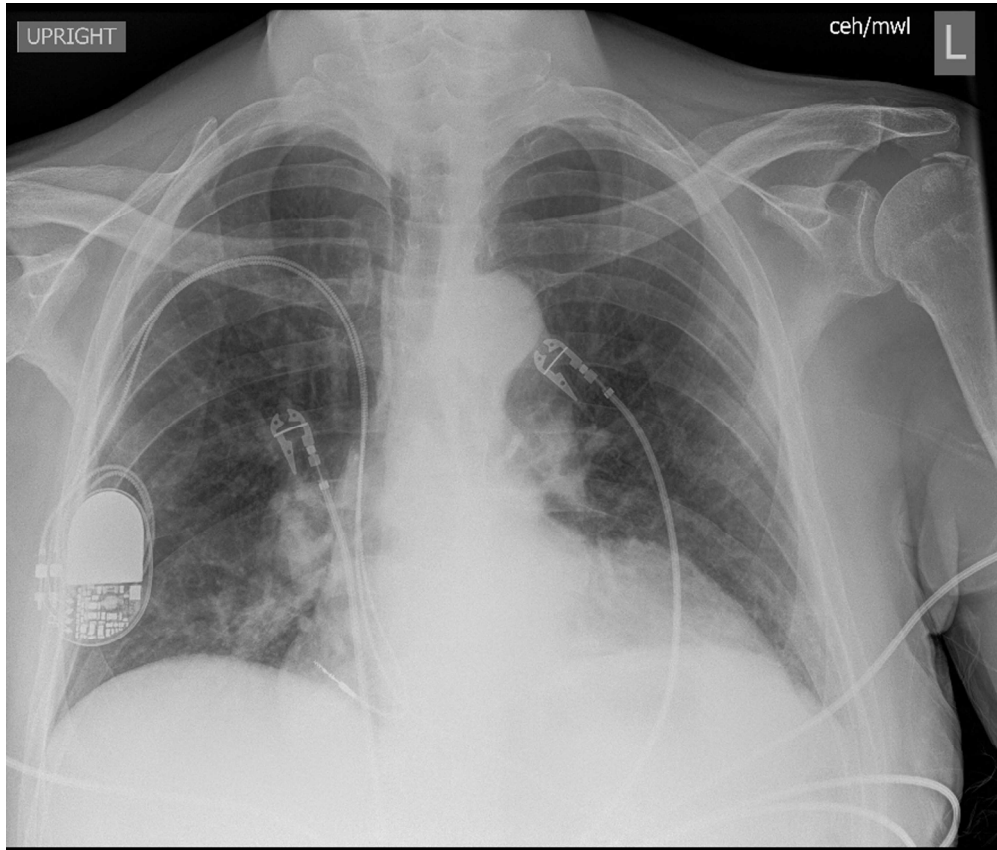


Figure 4: Portable CXR taken in the Emergency Department during assessment for acute pneumonia reveals low lung volumes and what was assumed to be resultant crowding of pulmonary parenchyma in both lung bases medially. The interpretation at that time was that there was no acute pneumonia.

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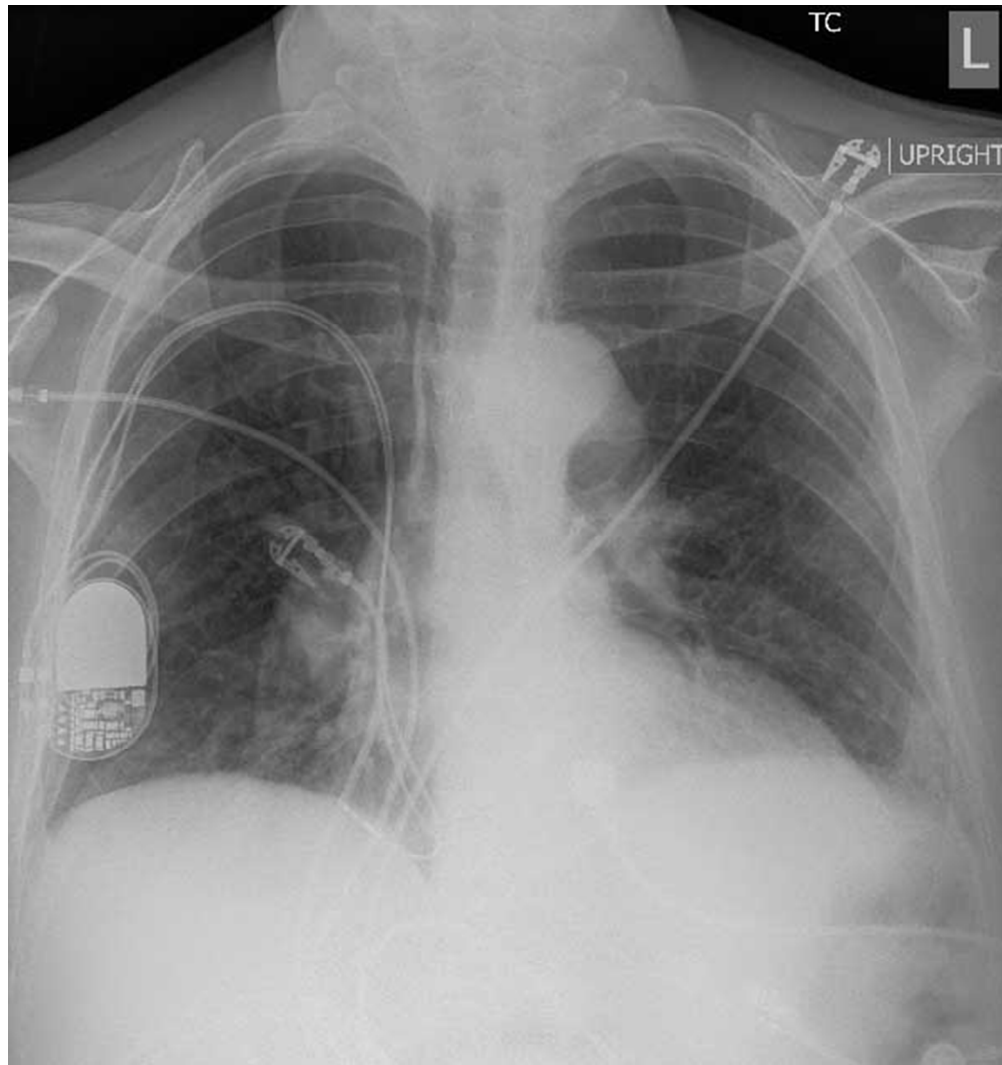


Figure 5: This CXR was performed 5 days before the CXR in Figure 4. The lung volumes are comparably low, but the small opacity in the right infrahilar region on Figure 4 is not present. This indicates that there was a pneumonia in the right lung base on the CXR in Figure 4 rather than normal crowding of lung tissue.

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Figure 6: Same image as figure 4 with the right infrahilar pneumonia indicated by arrows.

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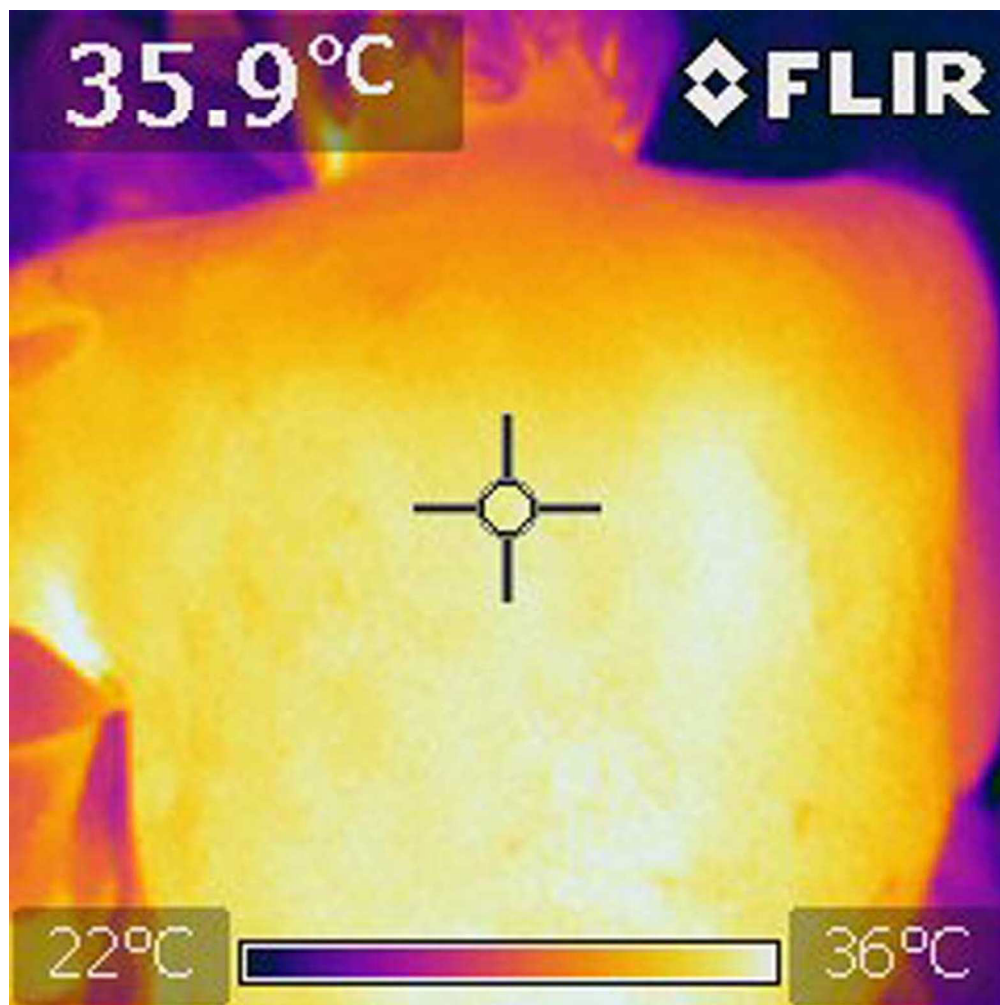


Figure 7: TI obtained shortly after the CXR shown in Figure 4. The image is taken from the patient's back so that the patient's right is on the viewer's right. There is an area of increased heat (white area) in the right lung base concordant with that seen in Figure 4.

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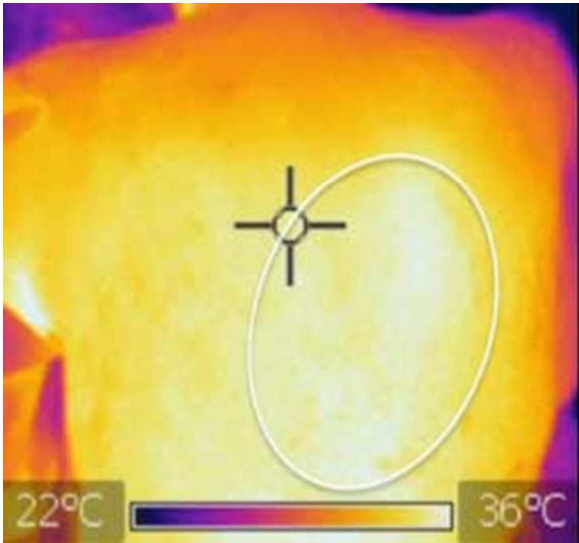


Figure 8: Same image as Figure 7 with the area of pneumonia (white area) encircled by an oval ring.

24x22mm (300 x 300 DPI)

review only

Items to include when reporting a randomized trial in a journal or conference abstract

Item	Description	Reported on line number
Title	Identification of the study as randomized	1
Authors *	Contact details for the corresponding author	4 - 7
Trial design	Description of the trial design (e.g. parallel, cluster, non-inferiority)	132; 245
Methods		
Participants	Eligibility criteria for participants and the settings where the data were collected	139-153
Interventions	Interventions intended for each group	149-151, 168--188;
Objective	Specific objective or hypothesis	91-92; 126- 129; 257
Outcome	Clearly defined primary outcome for this report	185-189
Randomization	How participants were allocated to interventions	133; 149
Blinding (masking)	Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment	185-189
Results		
Numbers randomized	Number of participants randomized to each group	155
Recruitment	Trial status	
Numbers analysed	Number of participants analysed in each group	155-158
Outcome	For the primary outcome, a result for each group and the estimated effect size and its precision	258,291-297, 344
Harms	Important adverse events or side effects	
Conclusions	General interpretation of the results	427-435
Trial registration	Registration number and name of trial register	NA
Funding	Source of funding	Funding: The Bacca Foundation and the Consortium for Affordable Medical Technologies (CAMTech) (Fund # is 223707)

*\*this item is specific to conference abstracts*

# BMJ Open

## Similarity of Chest X-ray and Thermal Imaging of Focal Pneumonia: A Randomized Proof of Concept Study at a Large Urban Teaching Hospital

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Manuscripts

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3 1 Similarity of Chest X-ray and Thermal Imaging of Focal Pneumonia: A randomized  
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5 2 proof of concept study at a large urban teaching hospital.  
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26 39 ABSTRACT  
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30 41 Objective: To assess the diagnostic accuracy of thermal imaging (TI) in the setting  
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32 42 of focal consolidative pneumonia with chest x-ray (CXR) as the gold standard.  
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36 44 Setting: A large, 973 bed teaching hospital in Boston, Massachusetts  
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40 46 Participants: 47 patients enrolled, 15 in a training set, 32 in a test set. Age range  
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42 47 10 months – 82 years (median = 50 years)  
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45

46 49 Materials and Methods: Subjects received CXR with subsequent TI within 4 hours of  
47  
48 50 each other. CXR and TI were assessed in blinded random order. Presence of focal  
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50 51 opacity (pneumonia) on CXR, the outcome parameter, was recorded. For TI,  
51  
52 52 presence of area(s) of increased heat (pneumonia) was recorded. Fisher's exact test  
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54 53 was used to assess the significance of the correlations of positive findings in the  
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56 54 same anatomic region.  
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56 Results: With TI compared to the CXR (the outcome parameter), sensitivity was  
57 80.0% (95% Confidence intervals (95% CI): [29.9%, 98.9%], specificity was 57.7%  
58 (95% CI: [37.2%, 76.0%]). Positive predictive value of TI was 26.7% (95% CI:  
59 [8.9%, 55.2%]) and its negative predictive value was 93.8% (95% CI: [67.7%,  
60 99.7%]).

61

62 Conclusions: This feasibility study confirms proof of concept that chest TI is  
63 consistent with CXR in suggesting similarly localized focal pneumonia with high  
64 sensitivity and negative predictive value. Further investigation of TI as a point of  
65 care imaging modality is warranted.

66

67 Strengths and Limitations:

68

69 Strengths:

- 70 • Proof of concept suggesting that Thermal Imaging (TI) is a valid, innovative,  
71 and inexpensive technology useful for diagnosing bacterial pneumonia
- 72 • Proof of concept suggesting that Thermal Imaging (TI) is a rapid means of  
73 diagnosing focal pneumonia in high throughput settings
- 74 • Proof of concept suggesting that Thermal Imaging (TI) is a valid and  
75 innovative technology useful in diagnosing pneumonia in resource limited  
76 regions of the world

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78 Limitations:

- 79 • As this is a proof of concept study, it does not have adequate power to be  
80 definitive and cannot replace chest xray for detecting focal pneumonia

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4 81 • As this is a proof of concept study, limitations of the technology have not  
5  
6 82 been fully discerned, and at present include adipose tissue and interpretation,  
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8 83 but may include other concerns which will require higher numbers of patients  
9  
10 84 enrolled.

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12  
13 85 Word Count: 2849

- 14  
15 86• Data Sharing: There are no additional unpublished data from the study.  
16  
17 87 Data are available to any researcher who is interested in the data, and will be  
18  
19 88 able to be accessed through Dyad and/or through correspondence with the  
20  
21 89 contributing authors.  
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24 91

25 92 Introduction

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29 94 This study investigates the degree to which thermal imaging (TI) and chest x-ray  
30  
31 95 (CXR) are concordant in detecting similarly localized focal pneumonia. Often a  
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33 96 clinically challenging diagnosis, bacterial pneumonia remains a major cause of  
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35 97 morbidity and mortality worldwide, particularly in under-resourced environments (1-  
36  
37 98 3). Expert panels, including the World Health Organization (WHO), have formulated  
38  
39 99 algorithms to enhance clinical accuracy (4), typically focusing on aspects of the  
40  
41 100 medical history and physical examination to determine the likelihood of bacterial  
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43 101 pneumonia. Despite having these algorithms, CXR is generally performed to confirm  
44  
45 102 the diagnosis in severe infections (5-16). If TI results are similar to CXR, it might  
46  
47 103 substitute for CXR when CXR is not available. In resource-limited environments,  
48  
49 104 where 2/3 of the world's population has no access to diagnostic imaging (17-18), the  
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51 105 potential use of TI in point of care screening could aid decision making to treat for  
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53 106 pneumonia.  
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3 107 Point of care imaging utilizing ultrasonography to diagnose pneumonia is attracting  
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5 108 interest (19-20). However, ultrasonography requires costly equipment and specific  
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7 109 expertise for image acquisition and interpretation.  
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10 110  
11 111 Anecdotal reports suggest that TI has potential for detecting pneumonia (21-22).  
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13 112 These case reports and methodologies have not been subjected to systematic  
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15 113 blinded assessment. In this initial proof of concept investigation, we compared TI to  
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17 114 CXR in patients suspected of having acute pneumonia.  
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22 116 With recent advances in infrared technology and increasing use assessing home heat  
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24 117 loss, low-cost thermal cameras have become available, currently costing as little as  
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26 118 \$200-\$300 (Flir.com). Installation of shielded radiographic rooms can cost hundreds  
27  
28 119 of thousands of dollars. Portable x-ray units capable of performing CXR can cost as  
29  
30 120 little as \$600-\$800 (dotmed.com). If uninsured, patient cost of a CXR in the US is  
31  
32 121 \$200-\$400 or, if insured, a co-pay of \$10-\$50 (23).  
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34 122

35  
36 123 For TI there are no additional costs beyond cost of the camera. TI cameras are  
37  
38 124 portable and operate with rechargeable batteries. TI is essentially identical to taking  
39  
40 125 a "snap and shoot" photograph and can be done in seconds during the primary  
41  
42 126 patient encounter without the camera physically contacting the patient. Digital  
43  
44 127 storage and transfer of TI is simple, utilizing a memory card in the TI device that can  
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46 128 be uploaded to a computer.  
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51 130 This study presents a prospective comparison of TI to CXR using a commercially  
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53 131 available thermal camera to determine the similarity of TI and CXR in the setting of  
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55 132 possible focal pneumonia and thus proof of concept and feasibility of TI to detect  
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57 133 focal pneumonia.  
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5 135 Materials and Methods6  
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10 137 Subjects: Participants came from the Emergency Department of Massachusetts  
11 138 General Hospital (Boston, MA). On admission to the Emergency Department, adult  
12 139 patients and families of children who had CXR included for evaluation of pneumonia  
13 140 were approached to discuss study participation. Written informed consent and, when  
14 141 applicable, participant assent was obtained from all participants. Enrollment  
15 142 occurred Monday - Friday, 7:00am - 11:00pm when research staff was available.  
16 143 Partners Human Research Committee approved the HIPPA compliant study protocol  
17 144 (#2013P001247).

18  
19 145

20 146 In an initial Training Set, subjects were excluded if they had chronic lung disease,  
21 147 congestive heart failure, prior chest surgery or immunosuppression. In a subsequent  
22 148 TEST Set, these exclusions were not used. Patients had TI within 4 hours of CXR.  
23 149 Patients were male older than 28 days, or female older than 28 days and younger  
24 150 than 8 years. After age eight, only males were included because of concerns for  
25 151 modesty.

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28 153 Forty-seven patients were enrolled. The first 15, comprising the Training Set, were  
29 154 not included as a part of the study's statistical assessment. These 15 cases provided  
30 155 a spectrum of results with 10 concordant for focal pneumonia, 2 concordant for no  
31 156 focal pneumonia, and 3 discordant for pneumonia. The remaining 32 subjects  
32 157 comprised the TEST Set. Analysis of the TEST Set included 31 patients (28 males, 3  
33 158 females), one patient had no usable thermal images. Patient age ranged from 10  
34 159 months - 82 years (median = 50.0 years, (25th, 75th) quartiles = (11.5, 60.5  
35 160 years), with 8 subjects  $\leq$  18 years and 23 subjects  $>$  18 years.

161

162 Imaging and interpretation: The radiologist interpreting CXR and TI (RHC) is an

163 American Board of Radiology certified diagnostic radiologist and sub-certified

164 pediatric radiologist with 40 years experience.

165

166 CXRs were assessed in random order blinded to TI. If focal opacities were found, the

167 lobe(s) were recorded. The lobes involved were precisely determined with posterior-

168 anterior (PA) and lateral examinations. When only a portable anterior-posterior (AP)

169 image could be obtained, the lobe(s) involved was determined by lung zone and

170 presence/absence of silhouetting of the mediastinum. CXRs were taken in PA and

171 lateral projections (N = 19). If PA and lateral imaging could not be performed,

172 because of clinical care requirements, a portable AP image was acquired (N = 12).

173

174 TI of the chest were taken from the neck down, similar to CXR, with both posterior

175 and anterior views whenever possible (N = 29). If a patient was too ill to be

176 positioned for two views only 1 view was obtained. Depending on the patients'

177 condition and preferred position, 1 patient had a posterior view and 1 an anterior

178 view. Oblique images were not obtained since TI interpretation depends on

179 assessment of asymmetric heat distribution. TI were acquired with the commercially

180 available FLIR i7 infrared thermal camera (flir.com). The subject was encompassed

181 in the field of view; a "snapshot" was obtained so the patient's chest filled the field of

182 view with the entire chest from side to side included from the level of the shoulders

183 to bottom of the chest (or below). Patient to camera distance varied based on patient

184 size. Subjects could be sitting or recumbent with the chest exposed. Clothing was

185 removed from the chest prior to TI acquisition.

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3 187 The camera used in this study has a resolution of 19,600 pixels detecting a  
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5 188 temperature range -4° Fahrenheit - 482° Fahrenheit (-20° Celsius - 250° Celsius)  
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7 189 with sensitivity to 0.1 degree Celsius. Images filled the 2.8 inch LCD TI screen. TI  
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9 190 were interpreted while displayed on a desk top computer at a size comparable to the  
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11 191 size of the CXR, filling roughly 50% of the computer monitor screen. TI image size  
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13 192 varies depending on the imaging device. TI stored in the camera's memory can be  
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15 193 uploaded to a computer and displayed at whatever size preferred.  
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18 194

19 195 TI were evaluated in random order blinded to CXR. Any area(s) of increased heat  
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21 196 were recorded as upper, mid or lower lung zone, and identified as in the right or left  
22  
23 197 lung. (figures 1,2,3). Following initial assessment of blinded TI and CXR, to shed  
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25 198 light on possible causes for TI/CXR discrepancies, cases with disagreement were  
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27 199 reviewed in non-blinded fashion, using prior CXR when available.  
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35 205 (INSERT FIGURES 1, 2, 3)  
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Legend

Figure 1: CXR shows an opacity in the right lung base consistent with pneumonia.

Figure 2: TI obtained shortly after the CXR (Figure 1). The image is taken from the

patient's back so that the patient's right is on the viewer's right. There is an area of  
increased heat (white area) in the right lung base concordant with the CXR.

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3 213 Figure 3: Same image as Figure 2 with the area of pneumonia (white area) encircled  
4 by an oval ring.  
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222 TI is similar to nuclear medicine imaging in that it is not the precise size,  
223 configuration or margins that are of importance, but rather the temperature pattern  
224 with presence or absence of focal areas of increased heat, "hot spots," that is  
225 informative for focal pneumonia. Heat emanating from the patient's skin determines  
226 the TI image. Generalized skin temperature does not affect TI recognition of a hot  
227 spot. Since clothing recently removed from the chest might affect skin temperature  
228 globally but not focally, it is unlikely that previously removed clothing would affect  
229 recognition of a hot spot. Areas of symmetric increased heat were considered to  
230 represent normal variation in heat pattern and areas of increased heat over the  
231 neck, sternum, supraclavicular space, spine and axillae were determined to be  
232 normal on the initial 15 training cases. Abdominal heat pattern is similar to that of  
233 the chest without focal temperature changes relating to abdominal viscera. Unlike  
234 CXR, TI does not require that patients hold their breath. Therefore, minor patient  
235 motion will have minor, if any, effect on TI quality.

236

237 Statistical Methods: Paired data were constructed for each patient with CXR the  
238 standard for disease and TI the test variable. Each image was dichotomized as  
239 normal or showing focal pneumonia. TI sensitivity, specificity, positive predictive

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3 240 value and negative predictive value and their respective 95% confidence intervals  
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5 241 were estimated. Agreement between CXR and TI (modeled as a binary outcome with  
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7 242 agreement = 1 and disagreement = 0) and as a function of patient age and sex was  
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9 243 assessed using simple logistic regression models, as well as 2X2 contingency tables  
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11 244 with age dichotomized as >18 years for adults and  $\leq$  18 years for children. Fisher's  
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13 245 exact test was used to assess significance of correlation between age (or sex) and  
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15 246 similarity between CXR and TI. Finally, despite the small sample, Cohen's kappa was  
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17 247 also used as an imperfect measure of agreement between the two modalities (24,  
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19 248 25). A significance level of 0.05 was assumed.  
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## 24 250 Results

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28 252 This study assessed the diagnostic sensitivity and specificity of TI using the chest  
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30 253 CXR as the gold standard. . For the overall cohort, five patients were identified as  
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32 254 having focal pneumonia by CXR and 26 not. For the pediatric cohort, there were 2  
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34 255 with focal pneumonia, 6 without by CXR.  
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38 256  
39 257 Eleven cases were TI positive and CXR negative (false positives). One case was TI  
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41 258 negative and CXR positive (false negative).  
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43 259  
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45 260 Table 1 summarizes the TI sensitivity, specificity, positive predictive value, negative  
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47 261 predictive values and their corresponding 95% confidence intervals (95% CI). .  
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	True Positive	True Negative	False Positive	False Negative	Sensitivity (95% CI)	Specificity (95% CI)	Positive Predictive Value	Negative Predictive Value
TI vs blinded CXR (3 positive, 26 negative)	4	15	11	1	80.0% (29.9%, 98.9%)	57.7% (37.2%, 76.0%)	26.7% (8.9%, 55.2%)	93.8% (67.7%, 99.7%)

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263 Table 1: Sensitivity analysis of TI assuming the CXR as the gold standard. 95%

264 Confidence intervals (95% CI) are included for all parameters.

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267 The relationship between TI and CXR agreement with patient demographics was  
 268 assessed using logistic regression models and simple contingency tables. There was  
 269 no significant association between modality agreement and patient age (treated as a  
 270 continuous variable or dichotomized as adult versus pediatric) or sex (age:  $p = 0.3$   
 271 (95% CI for the regression coefficient = (-0.01, 0.004), odds ratio (OR) = 0.99, 95%  
 272 CI = (0.99, 1.00)]; sex:  $p = 0.16$  [95% CI = (-0.16, 1.05), OR = 1.53, 95% CI =  
 273 (0.85, 2.85)]. Similar results were obtained when individual contingency tables for  
 274 sex ( $p = 0.54$ ) or dichotomized age (>18 versus  $\leq 18$  years;  $p = 0.53$ ) were used.  
 275 Despite its limitations in small samples (24, 25), Cohen's kappa was also estimated  
 276 as an imperfect measure of agreement between TI and CXR [ $\kappa = 0.21$ , 95% CI =  
 277 (-0.1421, 0.5591)]. Even when CXRs were unblinded,  $\kappa = 0.48$  [95% CI =  
 278 (0.16, 0.79)]. The wide 95% confidence intervals are a further indication of the  
 279 limitations of kappa to quantify agreement in small samples.



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6 281 Since this is an exploratory proof of concept study the sample size is not based on  
7 282 statistical power. In order to achieve a power of 0.80, with the conditions  
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9 283 encountered in this study, a power calculation showed 138 patients would be  
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11 284 required. Furthermore, the sample size required to detect even modest agreement  
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13 285 quantified by kappa is  $n \geq 40$  patients.  
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17 287 To investigate causes for TI/CXR discrepancies, cases with disagreement were  
18 288 reviewed in a non-blinded fashion, using prior and subsequent CXR (comparison  
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20 289 images were not included in the blinded, original CXR assessments). This review of  
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22 290 discrepant cases is not included in the study's statistical analysis.  
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28 292 For the 11 false positive TI cases, prior CXRs were available in only three cases.  
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30 293 Each of these 3 cases had diffuse findings confounding CXR interpretation. One had  
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32 294 diffuse changes of cystic fibrosis, one had changes of chronic obstructive pulmonary  
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34 295 disease and one had low lung volumes. When CXR was reviewed with prior CXR, the  
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36 296 CXR interpretation was changed to focal pneumonia (figure 4,5,6) concordant with TI  
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38 297 (figure 7,8) in each instance. Follow-up images provided no additional information.  
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40 298 (INSERT FIGURES 4, 5, 6, 7, 8)  
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54 305 Legend  
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3 306 Figure 4: Portable CXR taken in the Emergency Department during assessment for  
4 acute pneumonia reveals low lung volumes and what was assumed to be resultant  
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6 crowding of pulmonary parenchyma in both lung bases medially. The interpretation  
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8 at that time was that there was no acute pneumonia.  
9 309  
10 310

11  
12 311 Figure 5: This CXR was performed 5 days before the CXR in Figure 4. The lung  
13 volumes are comparably low, but the small opacity in the right infrahilar region on  
14 312  
15 Figure 4 is not present. This indicates that there was a pneumonia in the right lung  
16 313  
17 base on the CXR in Figure 4 rather than normal crowding of lung tissue.  
18 314  
19 315

20 316 Figure 6: Same image as figure 4 with the right infrahilar pneumonia indicated by  
21 317  
22 arrows.  
23 318

24 319 Figure 7: TI obtained shortly after the CXR shown in Figure 4. The image is taken  
25 320  
26 from the patient's back so that the patient's right is on the viewer's right. There is  
27 321  
28 an area of increased heat (white area) in the right lung base concordant with that  
29 322  
30 seen in Figure 4.  
31 323

32 324 Figure 8: Same image as Figure 7 with the area of pneumonia (white area) encircled  
33 325  
34 by an oval ring.  
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36 327  
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38 328 For 2 other cases, knowledge of TI findings resulted in a change in the CXR  
39 329  
40 interpretation. For one case, the CXR interpretation was changed to a faint opacity,  
41 330  
42 consistent with focal pneumonia and in one case, there was the question of a very  
43 331  
44 subtle opacity, both concordant with the TI images.  
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3 333 Three other CXRs had what appeared to be atelectasis in regions of TI hot spots. In  
4  
5 334 light of the TI results, these areas of presumed atelectasis may actually represent  
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7 335 pneumonia. These opacities on CXR were, in one case each, in the right upper lobe,  
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9 336 left upper lobe and left lower lobe.  
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14 338 Three of the 11 false positive TI cases had no change in CXR interpretation.

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18 340 The one false negative case had no change to TI or CXR interpretation.

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22 342 There were no tumors, pulmonary edema or other abnormalities identified on CXR  
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24 343 that might affect TI results.  
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28 345 Non-blinded review produced no changes in interpretation of TI images.  
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32 347 Discussion  
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37 349 This study suggests that TI is sensitive and modestly specific compared to CXR in  
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39 350 detecting focal pneumonia.  
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43 352 There currently is no experimental data assessing the mechanism of increased focal  
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45 353 heat, as detected by TI, associated with focal pneumonia. The assumption is that  
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47 354 the focal hyperemia associated with focal inflammation, in this case pneumonia,  
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49 355 produces focally increased heat. It presumably is this increased heat radiating from  
50  
51 356 the site of pneumonia that is detected by TI. Consequently, an area of atelectasis  
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53 357 which is not associated with hyperemia, will not produce an area of focally increased  
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55 358 heat.  
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3 360 It is focal increased heat that is the indicator of focal pneumonia on TI. Thus any  
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5 361 bacterial organism (which organism cannot be determined) may be the culprit. Viral  
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7 362 pneumonias are generally diffuse and do not typically generate a focal pneumonia.  
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10 363 Some atypical pneumonias, such as mycoplasma, may have a focal consolidative  
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12 364 component which might be detected as a hot spot. It has been reported in a case  
13  
14 365 report that acute consolidative tuberculosis caused a TI hot spot but sub-acute  
15  
16 366 tuberculosis did not (21). It is not the precise lobar distribution but rather presence  
17  
18 367 or absence of a focal hot spot that is the informative aspect of TI.  
19

20 368  
21  
22 369 The purpose of this study was to assess the sensitivity and specificity of TI , in  
23  
24 370 detecting a focal consolidation, using CXR as the gold standard given its wide use  
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26 371 for diagnosis of pneumonia (19, 20, 26-31), including studies assessing effectiveness  
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28 372 of the WHO clinical diagnostic criteria (31). Ultrasound is the only other point of care  
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30 373 imaging procedure widely studied for diagnosis of pneumonia and in virtually all of its  
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32 374 validation studies it is compared to CXR (28-30). While clinical signs and symptoms  
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34 375 have been utilized, collecting accurate data and correlation with the ultimate  
35  
36 376 diagnosis of pneumonia is inconsistent (32). However, it is not the purpose of this  
37  
38 377 study to assess the accuracy of imaging to detect pneumonia as compared to the  
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40 378 clinical diagnosis. Ultimately, other methodologies such as inflammatory markers  
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42 379 may play a role, but currently these are in relatively early stages of development.  
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47 381 Accuracy of CXR in determining the presence of focal pneumonia will vary depending  
48  
49 382 on quality of imaging and experience of the observer, as is true for TI. Although  
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51 383 computerized tomography (CT) has greater accuracy in detecting pneumonia than  
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53 384 CXR (33-34), CT cannot be used as routine imaging for pneumonia because of  
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55 385 concerns of radiation exposure and cost (31).  
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3 387 There was only one false negative in the cohort of 31 patients with 11 false positives  
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5 388 (sensitivity = 0.80, specificity = 0.58). Thus the ability of TI to accurately detect  
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7 389 focal pneumonia (as determined by CXR), in this cohort was relatively high. For a  
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9 390 screening test, this ability to not miss focal pneumonia is the most critical criterion.  
10  
11 391 The higher rate of false positives would lead to either over-treating or further testing  
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13 392 in a limited number of patients, which, although important, is a less critical issue.  
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15 393 The changes in CXR interpretation on non-blinded review of discrepant TI/CXR  
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17 394 revealed the following. 1) TI had hot spots in cases where CXR findings were initially  
18  
19 395 not definitive for focal pneumonia (N = 5). For two, CXR diagnosis was confounded  
20  
21 396 by pre-existing chronic lung diseases and in one by shallow inflation. For two others,  
22  
23 397 the suggestion of focal pneumonia on CXR was too subtle for definitive diagnosis. 2)  
24  
25 398 TI revealed hot spots in cases where the blinded CXR suggested atelectasis (N = 3).  
26  
27 399 This suggests that TI may be able to detect focal pneumonia in cases where pre-  
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29 400 existing lung disease or imaging technique confound the diagnosis on CXR or when  
30  
31 401 diagnosis on CXR is too subtle to be convincing (as possibly with early onset or  
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33 402 resolving focal pneumonia). TI may be able to differentiate between focal  
34  
35 403 pneumonia and atelectasis.  
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39 405 These findings suggest TI may be comparable to CXR in recognizing focal  
40  
41 406 pneumonia. Relatively low cost and portability of thermal cameras, some of which  
42  
43 407 can be used with mobile phones, potentially enable TI as a point of care screening  
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45 408 tool for focal pneumonia. Other advantages include minimal training to perform  
46  
47 409 images, lack of ionizing radiation exposure, off-site interpretation of digitized images  
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49 410 and possible software interpretation algorithms. Lack of physical contact with the  
50  
51 411 patient enhances infection control. Possible additional uses include following  
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53 412 progression of disease in combination with other modalities such as respiratory rate  
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55 413 and oximetry.  
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5 415 Limitations of TI include learning to interpret TI, presence of prior disease affecting  
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7 416 TI and the possibility that increased adiposity may interfere with its accuracy.  
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11 418 Conclusions

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16 420 This feasibility study confirms proof of concept that TI can demonstrate focal  
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18 421 pneumonia. Therefore, these findings support further investigation with larger trials  
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20 422 of patients that will be adequately powered to robustly assess the similarity between  
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22 423 TI and the outcome parameter. This technology is potentially most useful in  
23  
24 424 resource-limited environments where pneumonia is the second most common cause  
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26 425 of death in young children and where CXR equipment and expert readers are  
27  
28 426 unavailable (35). It also could be of benefit in high throughput healthcare settings,  
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30 427 such as emergency departments or busy doctors' offices and rural areas where  
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32 428 access to CXR is limited.  
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19 **Contributor ship Statement:**

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626 Tables

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	True Positive	True Negative	False Positive	False Negative	Sensitivity (95% CI)	Specificity (95% CI)	Positive Predictive Value	Negative Predictive Value
TI vs blinded CXR (5 positive, 26 negative)	4	15	11	1	80.0% (29.9%, 98.9%)	57.7% (37.2%, 76.0%)	26.7% (8.9%, 55.2%)	93.8% (67.7%, 99.9%)

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631 Table 1: Sensitivity analysis of TI assuming the CXR as the outcome parameter.

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3 637 Figure Legends  
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10 640 Figure 1: CXR shows an opacity in the right lung base consistent with pneumonia.  
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14 642 Figure 2: TI obtained shortly after the CXR (Figure 1). The image is taken from the  
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16 643 patient's back so that the patient's right is on the viewer's right. There is an area of  
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18 644 increased heat (white area) in the right lung base concordant with the CXR.  
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22 646 Figure 3: Same image as Figure 2 with the area of pneumonia (white area) encircled  
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24 647 by an oval ring.  
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30 650 Figure 4: Portable CXR taken in the Emergency Department during assessment for  
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32 651 acute pneumonia reveals low lung volumes and what was assumed to be resultant  
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34 652 crowding of pulmonary parenchyma in both lung bases medially. The interpretation  
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36 653 at that time was that there was no acute pneumonia.  
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40 655 Figure 5: This CXR was performed 5 days before the CXR in Figure 4. The lung  
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42 656 volumes are comparably low, but the small opacity in the right infrahilar region on  
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44 657 Figure 4 is not present. This indicates that there was a pneumonia in the right lung  
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46 658 base on the CXR in Figure 4 rather than normal crowding of lung tissue.  
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53 661 arrows.  
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3 663 Figure 7: TI obtained shortly after the CXR shown in Figure 4. The image is taken  
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5 664 from the patient's back so that the patient's right is on the viewer's right. There is  
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7 665 an area of increased heat (white area) in the right lung base concordant with that  
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9 666 seen in Figure 4.  
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14 668 Figure 8: Same image as Figure 7 with the area of pneumonia (white area) encircled  
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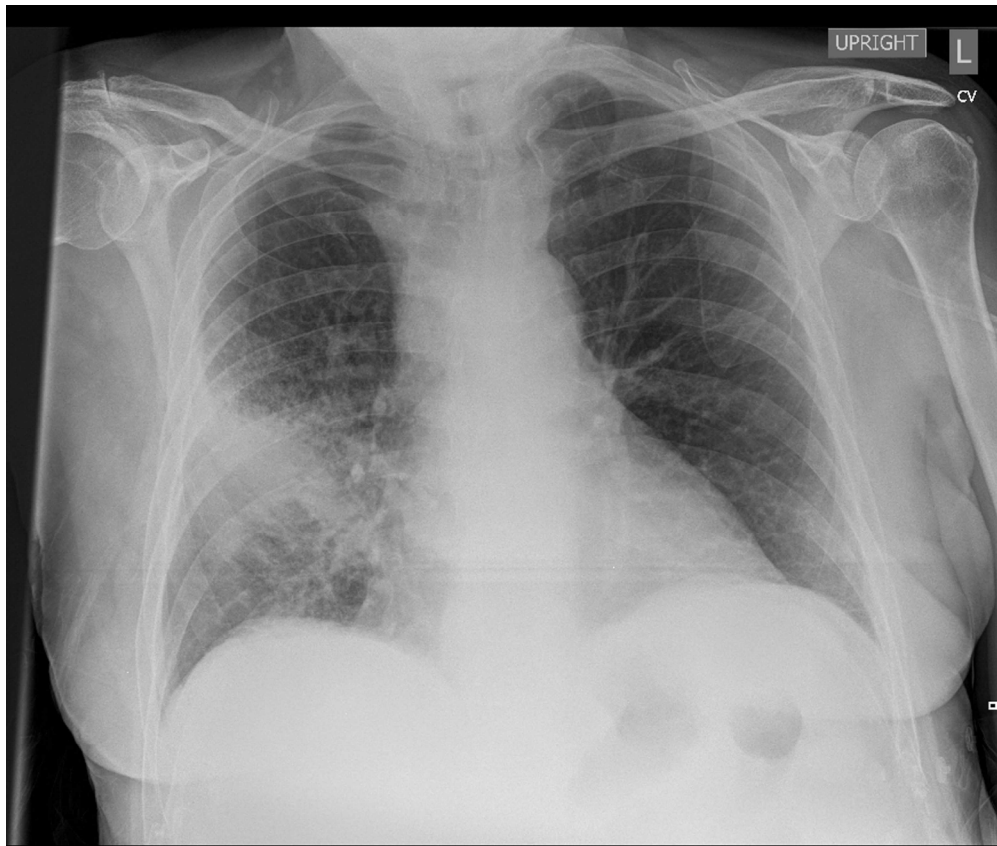


Figure 1: CXR shows an opacity in the right lung base consistent with pneumonia.

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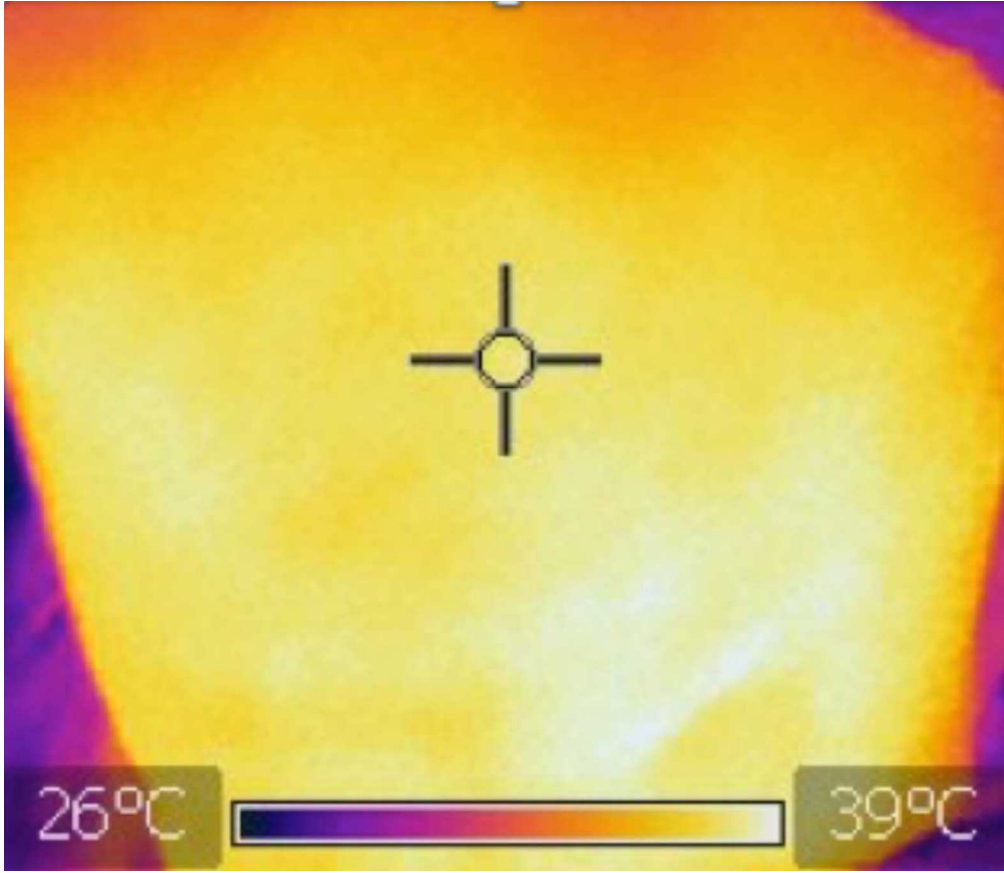


Figure 2: TI obtained shortly after the CXR (Figure 1). The image is taken from the patient's back so that the patient's right is on the viewer's right. There is an area of increased heat (white area) in the right lung base concordant with the CXR.

109x94mm (300 x 300 DPI)

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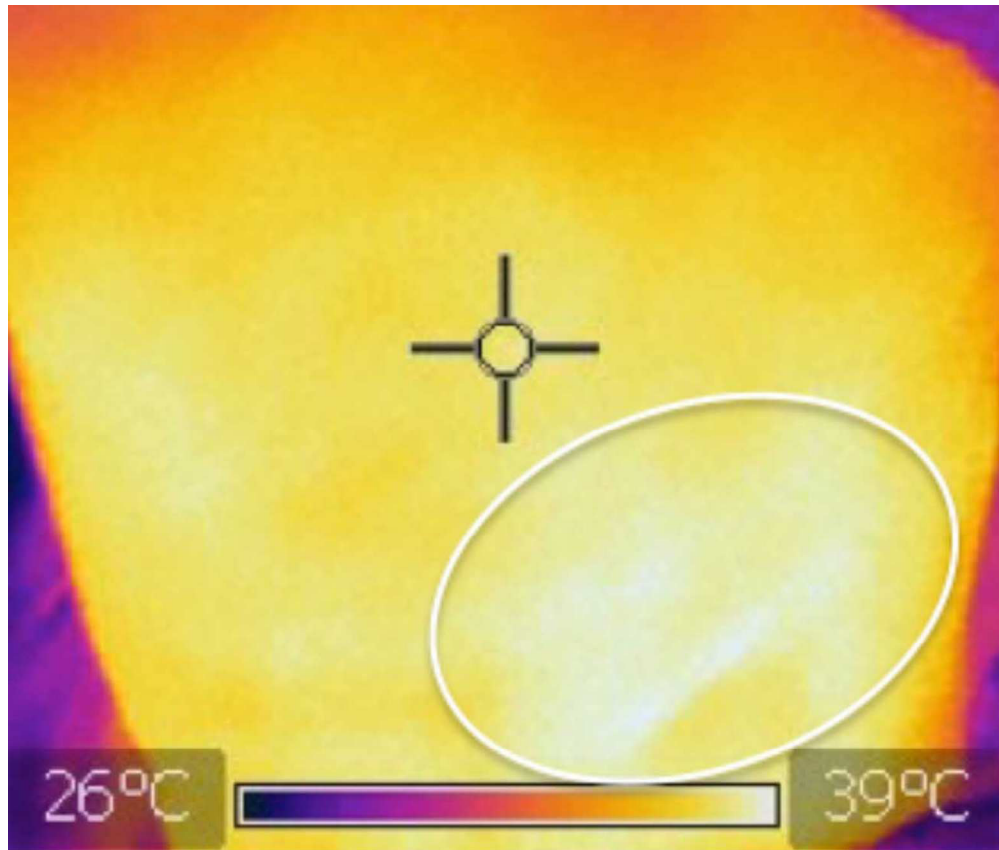


Figure 3: Same image as Figure 2 with the area of pneumonia (white area) encircled by an oval ring.

111x94mm (300 x 300 DPI)

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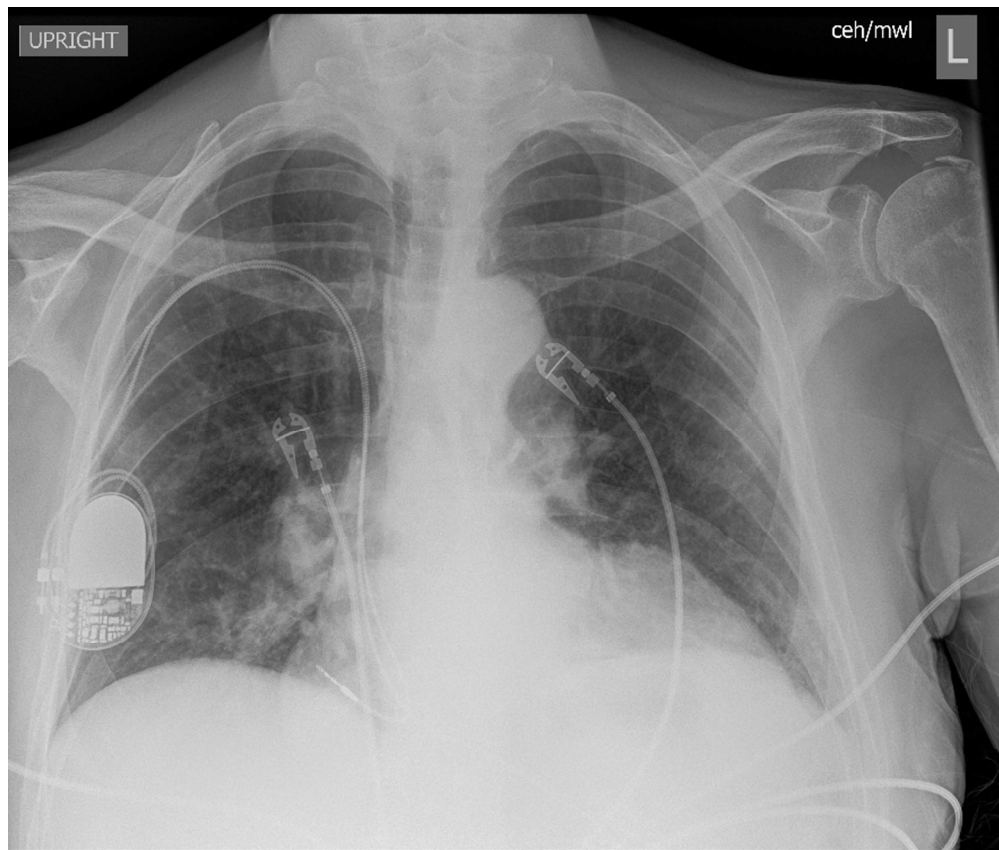


Figure 4: Portable CXR taken in the Emergency Department during assessment for acute pneumonia reveals low lung volumes and what was assumed to be resultant crowding of pulmonary parenchyma in both lung bases medially. The interpretation at that time was that there was no acute pneumonia.

311x264mm (300 x 300 DPI)

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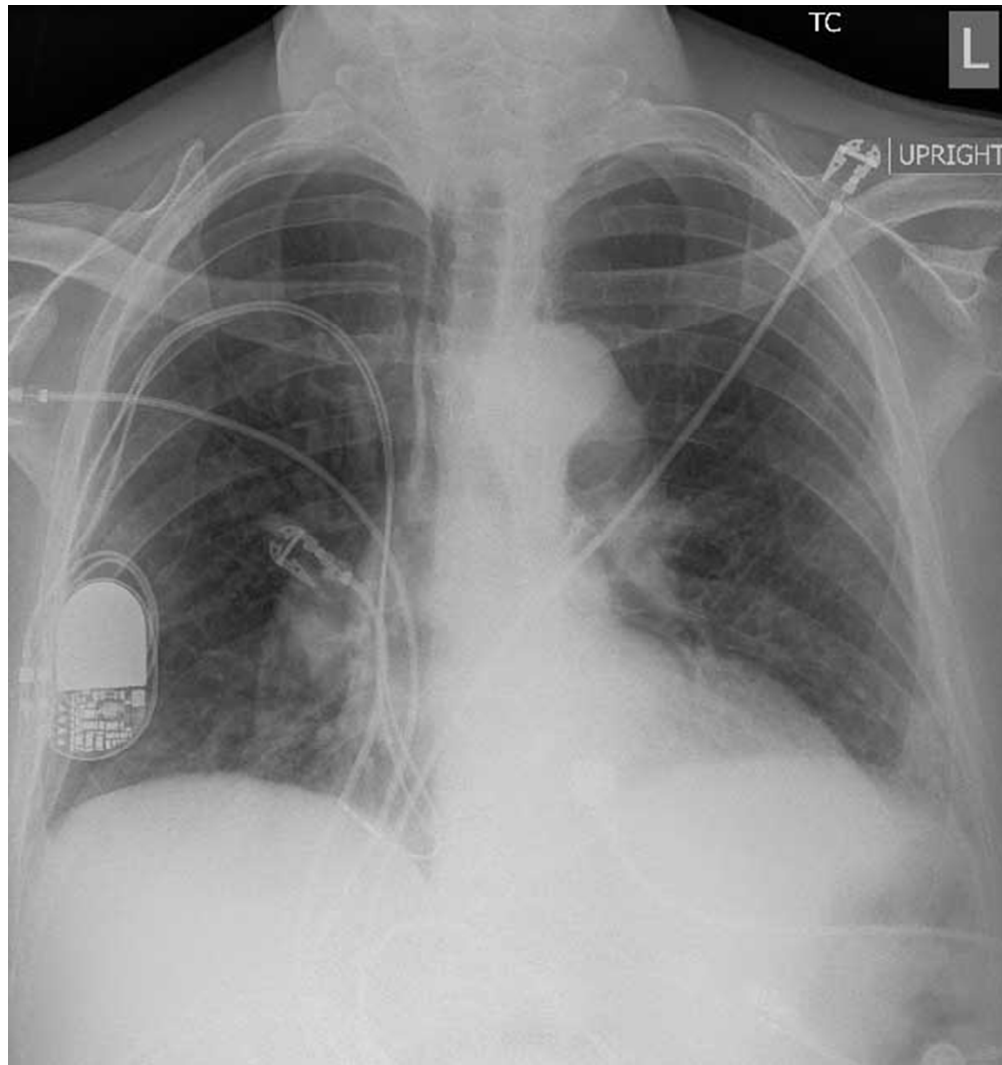


Figure 5: This CXR was performed 5 days before the CXR in Figure 4. The lung volumes are comparably low, but the small opacity in the right infrahilar region on Figure 4 is not present. This indicates that there was a pneumonia in the right lung base on the CXR in Figure 4 rather than normal crowding of lung tissue.

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Figure 6: Same image as figure 4 with the right infrahilar pneumonia indicated by arrows.

24x22mm (300 x 300 DPI)

review only

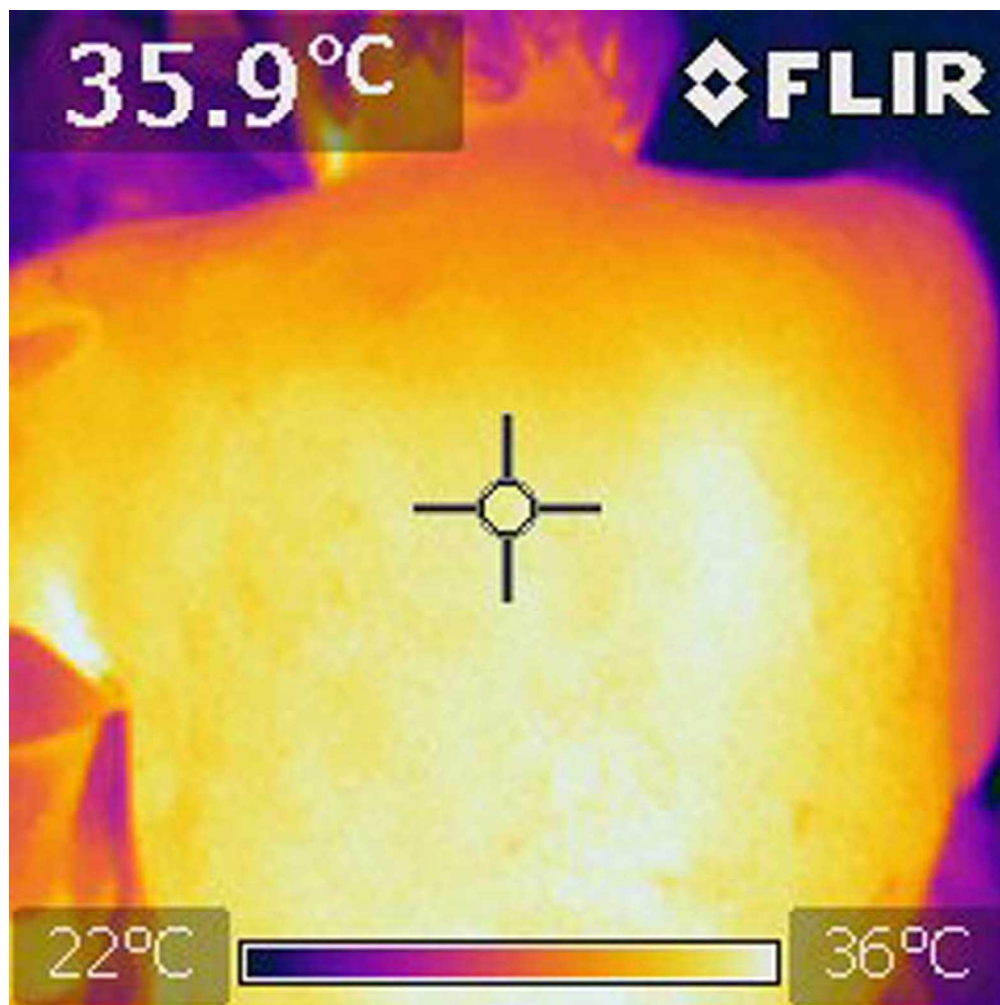


Figure 7: TI obtained shortly after the CXR shown in Figure 4. The image is taken from the patient's back so that the patient's right is on the viewer's right. There is an area of increased heat (white area) in the right lung base concordant with that seen in Figure 4.

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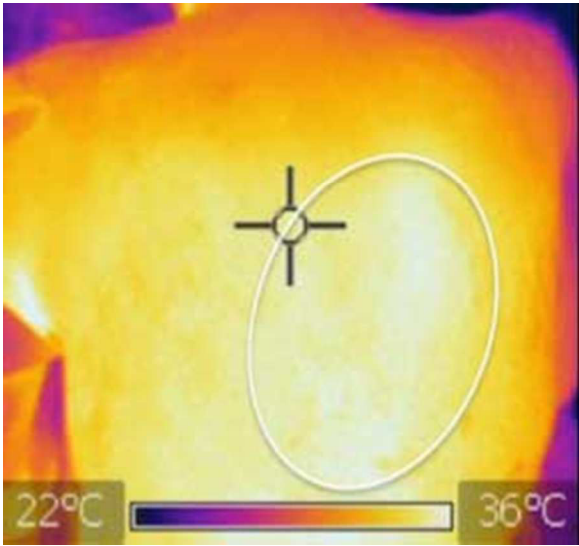


Figure 8: Same image as Figure 7 with the area of pneumonia (white area) encircled by an oval ring.

24x22mm (300 x 300 DPI)

review only

Items to include when reporting a randomized trial in a journal or conference abstract

Item	Description	Reported on line number
Title	Identification of the study as randomized	1
Authors *	Contact details for the corresponding author	4 - 7
Trial design	Description of the trial design (e.g. parallel, cluster, non-inferiority)	132; 245
Methods		
Participants	Eligibility criteria for participants and the settings where the data were collected	139-153
Interventions	Interventions intended for each group	149-151, 168--188;
Objective	Specific objective or hypothesis	91-92; 126- 129; 257
Outcome	Clearly defined primary outcome for this report	185-189
Randomization	How participants were allocated to interventions	133; 149
Blinding (masking)	Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment	185-189
Results		
Numbers randomized	Number of participants randomized to each group	155
Recruitment	Trial status	
Numbers analysed	Number of participants analysed in each group	155-158
Outcome	For the primary outcome, a result for each group and the estimated effect size and its precision	258,291-297, 344
Harms	Important adverse events or side effects	
Conclusions	General interpretation of the results	427-435
Trial registration	Registration number and name of trial register	NA
Funding	Source of funding	Funding: The Bacca Foundation and the Consortium for Affordable Medical Technologies (CAMTech) (Fund # is 223707)

*\*this item is specific to conference abstracts*