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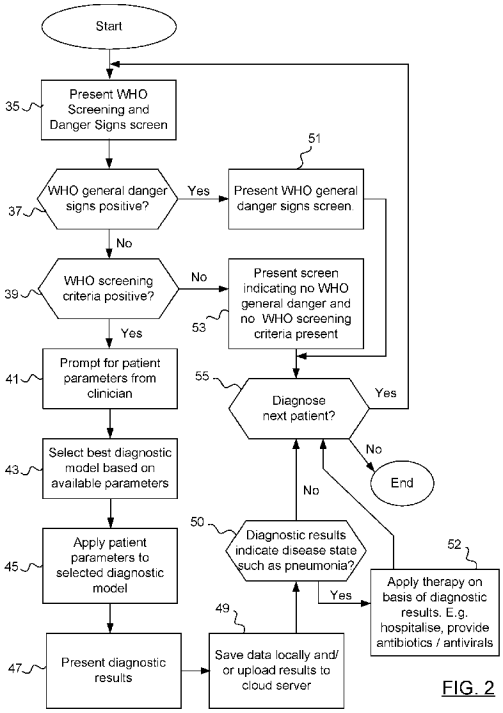

FIG. 2

(57) Abstract: A method of automatically diagnosing pneumonia in a patient includes using an input/output interface device to obtain values of two or more diagnostic parameters of the patient from a carer for the patient. The method includes using a processor coupled to the input/output interface to apply the two or more diagnostic parameters to an electronic memory storing a plurality of precompiled pneumonia diagnostic models to identify an optimal diagnostic model for making a diagnosis. The values of the two or more diagnostic signs are applied to the identified optimal diagnostic model to generate a diagnosis output. The input/output interface device is operated in accordance with the diagnosis output to indicate the presence or absence of pneumonia in the patient to the carer. The carer may use the diagnosis to provide appropriate care to the patient. The pneumonia diagnostic models are derived from investigation of a population of pneumonia positive and non-pneumonia subjects.

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A METHOD AND APPARATUS FOR AUTOMATIC DISEASE STATE DIAGNOSIS

TECHNICAL FIELD

The present invention concerns methods and apparatus for assisting medical staff to diagnose and manage patients suffering from respiratory dysfunctions such as pneumonia.

RELATED APPLICATIONS

This application claims priority from Australian provisional patent applications Nos. 2016903894 and 2016903896, both filed 26 September 2016, the disclosures of which are hereby incorporated herein in their entireties.

BACKGROUND ART

Any references to methods, apparatus or documents of the prior art are not to be taken as constituting any evidence or admission that they formed, or form part of the common general knowledge.

Pneumonia is one of the leading causes of mortality in children under five worldwide. It is estimated that 905,059 children below the age of five died from pneumonia globally in 2013 [ref 1]. It accounted for 14% of a total of 6.3 million child deaths around the world that year [1, 2]. The United Nations (UN) is aware of the issue and, through the Millenium Development Goal (MDG) 4 program, worked with countries globally to reduce the under-five mortality rate by two thirds in the period 1990 to 2015 [3-5].

Diagnostic tools used currently to diagnose pneumonia include stethoscopes and auscultation, chest X-ray, chest CT imaging, blood analysis, pulse oximetry, microbiology laboratory. There is no gold standard to diagnose pneumonia. The definitive diagnosis of childhood pneumonia, especially the early stage disease, is surprisingly difficult even in a hospital. Lung aspiration biopsy may be the most effective approach but it is clearly impractical for

clinical use. The clinical examination and chest auscultation with a stethoscope are the first steps in diagnosing childhood pneumonia. Auscultation requires a skilled physician, and even then cannot provide a sensitive or specific enough diagnosis. Chest X-ray is often used as an important reference standard in confirming a clinical diagnosis. However, X-rays may not be sensitive to early stage pneumonia or when the diseased part of the lung is not clearly visible on the image. In addition, normal X-ray may lead to poor specificity of diagnosis in the presence of lung scarring or congestive heart disease. X-ray CT imaging (Computed Tomography) and other laboratory analyses such as sputum tests, blood culture and C-reactive protein (CRP) tests may be needed to differentially diagnose pneumonia in some cases. None of the tests mentioned above can be used as a gold standard. In hospitals in the developed world, the 'reference standard' used is the clinical diagnosis aided with auscultation, radiology, laboratory and microbiology as needed. Often, the suspicion of pneumonia is enough to prescribe antibiotics. Even in a hospital, it is difficult to separate viral wheeze from viral pneumonia, for instance (viral pneumonia is the most common form of pneumonia).

Throughout the world, the differential diagnosis of pneumonia and other respiratory disease is a complicated problem. Other illnesses that need to be resolved are: bronchiolitis, asthma, viral wheeze, pneumonia, tracheobroncomalacia (TBM) and croup – all in children. Malaria and congestive heart disease too can be symptomatically similar. In general diagnosing them is quite difficult even in a hospital setting. Long term monitoring at a home/community setting is next to impossible.

In resource-poor areas of the world where pneumonia is rampant, it is also difficult to find trained healthcare personnel with expert auscultation and clinical skills. The management of pneumonia in such regions is largely dependent on community workers who visit remote communities.

In order to address these problems, the World Health Organization (WHO) has developed a simple clinical procedure to classify pneumonia in resource-limited regions. These classifications directly lead to interventions such as

antibiotic prescription and hospitalization. The WHO procedure uses the symptom of cough (and/or breathing difficulty) as the screening-in feature for pneumonia; breathing rate then determines if pneumonia exists. The disease will be further classified as severe pneumonia if symptoms such as chest recession are also present.

Even though the breathing rate based WHO procedures perform poorly, in remote areas where over 90% of childhood pneumonia occur, it is the main pneumonia classification methods used to determine treatment/referral decisions.

In the past, several studies have explored the performance of the WHO procedure and its variants in pneumonia diagnosis. They reported a reasonably high sensitivity (69–94%) but an unacceptably poor specificity (67-16%). Researchers have attempted to improve the specificity of the WHO criteria using different approaches. These include the augmentation of WHO procedure by considering fever and other symptoms of pneumonia (nasal flaring, poor sleep, chest in-drawing, cough lasting longer than two days etc.). These efforts resulted in a sensitivity and specificity within the range 20–90%, but higher specificities were achieved only at the cost of lower sensitivity and vice versa. They also suffer from the fact that the higher the complexity of measurements, the more difficult it is to train community workers to reliably implement the procedure in field visits.

The WHO procedure uses breathing rate as the key measurement. However, obtaining the breathing rate is notoriously difficult in children. A vast amount of resources have been committed by agencies such as the Bill & Melinda Gates Foundation, Unicef and WHO to develop breathing rate counters. See https://www.path.org/publications/files/TS_update_rr_counters.pdf for an example. In the manual diagnosis of pneumonia, different clinical signs and measurements are dichotomized for the ease of assessment by a clinician. For instance, breathing rates above age indexed thresholds are used to declare the existence of pneumonia. Clinicians may also note the existence/absence of cough, fever, chest-in-drawing etc.

An issue with using only cough sounds is the number of coughs required (5-10 cough events) for reliable analysis. It is known that infant patients may not readily cough when required in order to use it for analysis. Furthermore, as the patient's condition gets worse, it is also known that cough symptoms may vanish due to their having a weakened body.

It will therefore be realised that one of the key developments still missing in the global fight against pneumonia is the absence of a rapid, low cost diagnostic method/system[1, 8-14]. Diagnosing each case accurately and precisely is difficult even with state of the art equipment, and even more so in poor resource settings.

It is an object of the present invention to provide a method and apparatus for assisting in the diagnosis of a disease state such as pneumonia which is straightforward for a clinician to use and which addresses one or more of the above described problems of the prior art.

SUMMARY OF THE INVENTION

According to a first aspect of the present invention there is provided a method for automatically providing a carer of a patient with a disease state diagnosis of the patient including the steps of:

providing a diagnostic application software product including a multiplicity of diagnostic models derived from investigation of a population containing disease state positive and non-disease state subjects;

operating an input/output interface of an electronic device including a memory storing the software product to prompt the carer for identification of a number of disease diagnostic parameters and values therefor for the patient;

operating a processor of the electronic device to select one of the diagnostic models from the memory based on the identified disease diagnostic parameters;

operating the processor to apply the values of the disease diagnostic parameters to the selected diagnostic model; and

presenting a diagnosis to the carer on the input/output interface based upon results of the application of the parameters to the selected diagnostic model for the carer to use in providing therapy to the patient.

Preferably said diagnostic parameters comprise: breathing rate, existence of fever, existence of runny nose, number of days with runny nose, number of days with cough, existence of chest indrawing, temperature, BMI (body mass index), and oxygen saturation level;

In an embodiment of the invention the method includes selecting one of the diagnostic models with reference to one or more look up tables correlating diagnostic performance of models against available diagnostic parameters.

The method may include prompting for user choice of a diagnostic model optimized for "sensitivity", "specificity" or "accuracy" wherein the method includes operating the electronic device to select one of the diagnostic models taking into account the optimization choice.

In an embodiment the method includes operating the device to determine if the values of diagnostic parameters indicate patient danger signs.

The method may include checking if the diagnostic values for the patient indicate that the patient is presenting general danger signs according to World Health Guidelines.

The method may include saving diagnostic results to a remote server whereby diagnostic results may be saved and compared from a plurality of diagnostic devices.

In some embodiments of the invention the method includes prompting for recording of at least one patient cough sound.

The method may include requiring the recording of no more than two patient cough sounds.

Preferably the method includes applying the at least one patient cough sound to a cough feature extraction engine of the diagnostic application to generate cough features.

The patient cough features may be applied to the diagnostic model to assist the diagnosis.

In a preferred embodiment of the invention the diagnostic parameters comprise breathing rate, temperature, heart rate and cough sound analysis.

According to another aspect of the present invention there is provided a diagnostic device arranged to prompt a clinician to input diagnostic information for a patient and further arranged to automatically present a diagnosis to the clinician, the diagnostic device including:

an electronic memory storing instructions comprising a diagnostic application software product including a plurality of diagnostic models derived from investigation of pneumonia-positive and non-pneumonia subjects;

an electronic processor in communication with the electronic memory for executing the instructions;

a user interface responsive to the electronic processor for the processor to prompt for and receive the diagnostic information;

wherein the processor is configured by the diagnostic application in use to present a diagnosis of the patient with the user interface by applying the diagnostic information to at least one of said diagnostic models.

Preferably the diagnostic device includes a microphone and audio interface coupling the microphone to the electronic processor.

The diagnostic application may include a cough feature extraction engine and whereby in use the processor applies the cough sound to the cough feature extraction engine to produce cough features thereof.

In an embodiment of the invention the diagnostic device is configured by the diagnostic application in use to apply the cough features to the at least one of said diagnostic models.

According to a further aspect of the present invention there is provided a method of automatically diagnosing pneumonia in a patient comprising:

using an input/output interface device to obtain values of two or more diagnostic parameters of the patient from a carer for the patient;

said diagnostic parameters comprising: breathing rate, existence of fever, existence of runny nose, number of days with runny nose, number of days with cough, existence of chest indrawing, temperature, BMI (body mass index), and oxygen saturation level;

using a processor device operatively coupled to the input/output interface to apply the two or more diagnostic parameters to an electronic memory storing a plurality of precompiled pneumonia diagnostic models to thereby identify an optimal diagnostic model of said plurality;

applying the values of the two or more diagnostic signs to the identified optimal diagnostic model to generate a diagnosis output from the diagnostic model; and

operating the input/output interface device in accordance with the diagnosis output to indicate presence or absence of pneumonia in the patient to the carer, for use by the carer in providing care to the patient;

wherein the pneumonia diagnostic models are derived from investigation of a population of pneumonia positive patients and non-pneumonia positive subjects.

According to another aspect of the present invention there is provided a method for operating an electronic processor based electronic device to diagnose a disease state of a patient including the steps of:

installing a diagnostic application software product on the electronic device, the diagnostic application including a multiplicity of diagnostic models;

prompting for identification of a number of disease diagnostic parameters and values therefor for the patient;

operating the electronic device to select one of the diagnostic models based on the identified disease diagnostic parameters;

operating the electronic device to apply the values of the disease diagnostic parameters to the selected diagnostic model; and

presenting a diagnosis to the clinician based upon results of the application of the parameters to the selected diagnostic model.

BRIEF DESCRIPTION OF THE DRAWINGS

Preferred features, embodiments and variations of the invention may be discerned from the following Detailed Description which provides sufficient information for those skilled in the art to perform the invention. The Detailed Description is not to be regarded as limiting the scope of the preceding Summary of the Invention in any way. The Detailed Description will make reference to a number of drawings as follows:

Figure 1 is a block diagram of a diagnostic device according to an embodiment of the present invention shown in use.

Figure 2 is a flowchart of a method performed by the diagnostic device of Figure 1 in accordance an embodiment of the invention.

Figures 3 to 5 depict screens generated by the diagnostic device for detecting WHO general danger signs of a patient.

Figure 6 depicts a screen generated by the diagnostic device for a clinician to enter diagnostic information for a patient.

Figure 7 depicts a screen generated by the diagnostic device to confirm the entered diagnostic information to the clinician.

Figure 8 is a flowchart illustrating a diagnostic model selection procedure by the diagnostic device at box 43 of the flowchart of Figure 2.

Figure 9 is a flowchart illustrating a procedure of the diagnostic device during selection of the best diagnostic model.

Figure 10 depicts a screen generated by the diagnostic device whilst it is analyzing the diagnostic information.

Figure 11 depicts a screen generated by the diagnostic device presenting the results of the analysis to the clinician.

Figure 11A is a block diagram of a diagnostic device according to a further embodiment of the present invention which is arranged to take into account cough sounds of the patient.

Figures 11A to 11D are screens generated by the diagnostic device of Figure 11A for prompting for cough sounds of the patient and for analyzing and presenting diagnostic results for the patient.

Figure 12 is a flow diagram detailing the process used to analyse cough sound data for designing a diagnostic model for use in an embodiment of the present invention.

Figure 13 is a flow diagram illustrating a method for training a diagnostic model for use in an embodiment of the present invention.

Figure 14 comprises graphs representing mean Sn (sensitivity) and Sp (specificity) values from training models calculated from the age group 2-11 month. Frames from top to bottom are arranged by the number of features used to create the model: one (top), two (middle), and three features (bottom) taken at a time. n is the number of possible feature combinations using one, two, three features at a time. Significant improvements in specificity can be seen as more features were used.

Figure 15 comprises ROC curve analysis for the age group of 2-11 month. The solid line in each frame represents the mean ROC curve, formed over k-iterations. Crosses on each frame represent the SD of the Sn and 1- Sp at points shown. On each frame, the performance of WHO/IMCI procedure for resource-limited regions is graphically illustrated (see boxes). The center of the box indicates the mean performance, and the height and width of the box represent SD.

Figure 16 comprises ROC curve analysis for the age group of 12-60 month. The solid line in each frame represents the mean ROC curve, formed over k-iterations. Crosses on each frame represent the SD of the Sn and 1- Sp at points shown. On each frame, the performance of WHO/IMCI procedure for resource-limited regions is graphically illustrated (see boxes). The center of the

box indicates the mean performance, and the height and width of the box represent SD.

Figure 17 is a graph showing the training and testing performance of the two best LRM models for 2-11 months and 12-60 months age group. The best LRM models for 2-11 months group were models using runny nose/days with runny nose/breathing rate/temperature and runny nose/days with runny nose/breathing rate/heart rate features. As for the 12-60 months group, the best models were based on fever/days with cough/heart rate/chest indrawing and runny nose/days with runny nose/breathing rate/temperature feature combinations.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Referring initially to figure 1 there is shown a diagnostic device 1 according to an embodiment of the present invention. The diagnostic device 1 comprises a unique combination of hardware and software specifically designed to assist a clinician to diagnose, and so be able to treat, a disease state such as pneumonia. In the embodiment of the invention that is illustrated in figure 1 the device 1 includes one or more processors in the form of microprocessor 3 and an electronic memory 5 that is accessible to the microprocessor 3 and which stores instructions that are executable by the microprocessor 3 in order for the diagnostic device 1 to process diagnostic signs of a patient 2 and present a diagnosis to carer in the form of clinician 4. The Diagnostic application 6 includes a plurality of diagnostic models 20 which are stored in memory 5 and a model lookup table 22 which the microprocessor 3 uses to determine the most appropriate diagnostic model based on available diagnostic parameters for a patient 2. As is explained in Appendix B of this specification, with reference to Table 9, the Inventors drew on their quantitative research of over 131,000 combinations of features associated with pneumonia to arrive at the diagnostic models that are used.

The electronic memory 5 includes an operating system 8 such as the *Android* operating system or the *Apple iOS* operating system, for example, for

execution by the microprocessor 3. The electronic memory 5 also includes a diagnostic application software product 6 according to a preferred embodiment of the present invention.

The microprocessor 3 is in data communication with a plurality of peripheral assemblies 9 to 23, as indicated in Figure 1, via a data bus 7. The data bus consists of metal tracks which convey electrical data signals 13 between the various assemblies of the device 1. The diagnostic device 1 is able to establish voice and data communication with a voice and/or data communications network 31 via WAN/WLAN assembly 23 and radio frequency antenna 29.

Although the diagnostic device 1 that is illustrated in Figure 1 is microprocessor based it will be realised that it could also be implemented using other types of technology. For example it could be implemented using a Field Programmable Gate Array (FPGA) or discrete logic circuits.

The diagnostic device 1 requires no external physiological sensors, physical contact with patient 2 or access to communication network 31 to operate. As will be explained the method is automated and straightforward to use. In some embodiments the device 1 collects patient metadata, diagnosis and treatment / referral information (e.g. whether or not an antibiotic was dispensed) along with GPS coordinates at the site of the diagnosis. The device logs the information or will transfer it over a WAN data network, 31, e.g. the Internet, to a cloud server 33 when/if network 31 is available. In one embodiment the device makes it possible to track pandemics. It can also take into account developing epidemics in diagnosing patients by accessing geographical information stored in the cloud server 33 of the diagnosis of disease in other locations using similar devices.

Referring now to Figure 2, there is shown a flowchart of a method according to a preferred embodiment of the present invention, which the diagnostic device implements under the control of the instructions that are coded into the diagnostic application 6.

At box 35 of Figure 2, the microprocessor 3 operates an input/output interface in the form of LCD touch screen interface 11 to display a prompt for a user, e.g. clinician 4, to enter diagnostic parameters of patient 2. Figure 3 shows the diagnostic device 1 displaying a data entry screen 57 on LCD touch screen interface 11 for the clinician 4 to enter the patient parameters.

The diagnostic program 6 includes instructions based on the Inventors' finding that there are at least 17 patient parameters that may be of use in diagnosing a disease state, such as pneumonia as shown in Table 1A below:

Age	Months
Weight	Kg
Height	m
Breathing rate	Breaths/min
Heart rate	Beats/min
Temperature	°C
BMI	Number
Oxygen saturation	Percentage
Chest indrawing	Yes/No
Fever	Yes/No
Days with fever	Days
Cough	Yes/No
Days with cough	Days
Runny nose	Yes/No
Days with runny nose	Days
Breathing difficulty	Yes/No
Days with breathing difficulty	Days

Table 1A – Seventeen Diagnostic Parameters for Pneumonia

The Inventors have discovered that the most straightforward patient parameters to obtain and which are effective in determining the presence of a respiratory disease state such as pneumonia are the nine diagnostic parameters that are set out in table 1B below.

Code	Diagnostic Sign
A	Breathing rate
B	Fever
C	Existence of runny nose
D	Days with runny nose
E	Days with cough
F	Chest indrawing
G	Temperature
H	BMI
I	Oxygen saturation
-	Not used

Table 1B – Subset of Nine Important Patient Diagnostic Sign Parameters

A preferred embodiment of diagnostic device 1 is configured to operate in the World Health Organization (WHO) framework and this can be seen in the way that the screen 57 provides for the clinician 4 to select WHO Screening Criteria, namely "Cough" and "Difficulty Breathing" and also to enter WHO General Danger Signs as listed in screen 57. At box 37 of the flowchart of Figure 2, if the clinician 4 has indicated on screen 57 that the patient 2 is displaying WHO general danger signs then microprocessor control diverts to box 51 at which point the microprocessor 3 operates screen 59 (Fig. 4) to alert the clinician 4 that the patient 2 is indicating severe pneumonia or disease according to the WHO general danger signs criteria. Alternatively, if at box 37 the patients' parameters do not indicate the WHO general danger signs then control diverts to box 39. At box 39 the microprocessor checks whether the patient parameters indicate that the WHO criteria for further screening have been met. If they have not been met then control diverts to box 53 at which point the microprocessor 5 causes the screen 61 that is shown in Figure 5 to display thereby indicating to the clinician 4 that the patient 2 exhibits neither the WHO general danger signs nor the WHO screening criteria.

Alternatively, if at box 39 the microprocessor 5, executing a further instruction of diagnostic application 6, determines that the patient's parameters indicate that the WHO screening criteria parameters are met then control diverts to box 41.

At box 41 the microprocessor 5 causes screen 63 (Fig. 6) to display on LCD touchscreen 11 to prompt for patient diagnostic parameters from the clinician 4.

Screen 63 presents selection buttons 65A,..,65I for the nine patient parameters that have previously been referred to in Table 1B.

In the presently described embodiment the clinician 4 is required to select at least three of the diagnostic parameters of Table 1B by means of the selection buttons 65A..,65I. Control then diverts to box 43 (Fig. 2) wherein microprocessor 3 displays screen 67 (Fig. 7) on interface 11. In the presently described preferred embodiment of the invention screen 67 includes selection buttons 69, 71 and 73 for clinician 4 to indicate a preference for the diagnostic model that will be used to optimize for any one of diagnostic "sensitivity", "specificity" or "accuracy". These terms have the following meanings:

Sensitivity: (also called the true positive rate, the recall, or probability of detection in some fields) measures the proportion of positives that are correctly identified as such (e.g., the percentage of sick people who are correctly identified as having the condition).

Specificity: (also called the true negative rate) measures the proportion of negatives that are correctly identified as such (e.g., the percentage of healthy people who are correctly identified as not having the condition).

Accuracy: (ACC) = (Σ True positive + Σ True negative) / Σ Total population

At box 43, the microprocessor 3 selects the optimal diagnostic model, amongst models 20 which are stored in memory 5, based on the patient parameters that have been submitted. To select the best of models 20 for the information that the clinician has entered, the microprocessor 3, as configured by diagnostic program 6, queries diagnostic model lookup tables 22 which are stored in memory 5 and which the Inventors have produced. (It will be realised that in other embodiments of the invention, wherein a high power processor is used, it may be possible to generate the required information as required without resort to look up tables.)

The content of the diagnostic lookup tables 22 is set out as follows:

Table 2A– Patient 2 to 11 Months of Age – Diagnostic Model Ordered According to Descending Sensitivity.

Table 2B – Patient 2 to 11 Months of Age – Diagnostic Model Ordered According to Descending Specificity

Table 2C – Patient 2 to 11 Months of Age – Diagnostic Model Ordered According to Descending Specificity.

Table 3A – Patient 12 to 60 Months of Age – Diagnostic Model Ordered According to Descending Sensitivity

Table 3B – Patient 12 to 60 Months of Age – Diagnostic Model Ordered According to Descending Specificity.

Table 3C – Patient 12 to 60 Months of Age – Diagnostic Model Ordered According to Descending Accuracy.

The patient diagnostic sign parameters that make up each combination in the combination columns of the following Tables 2A to C have previously been defined in Table 1B.

	Ordered according to descending sensitivity					
No	**Combination**	***SEN (%)***	**SPE (%)**	**ACC (%)**	**PPV (%)**	**NPV (%)**
1	CEF-	***96***	50	77	74	81
2	EFI-	***94***	54	77	76	85
3	CDF-	***92***	52	74	74	73
4	CDEF	***92***	56	76	74	86

5	ACDI	***91***	70	82	82	89
6	ACFG	***91***	50	73	73	77
7	ABCD	***91***	61	77	76	88
8	ABI-	***91***	51	73	72	85
9	ABCI	***91***	51	73	72	85
10	BFI-	***91***	58	78	75	86
11	BCFI	***91***	58	78	75	86
12	BFGI	***91***	58	78	75	86
13	ACDH	***89***	64	77	78	74
14	CEFI	***89***	57	77	76	81
15	DEFI	***89***	55	76	74	81
16	ACDG	***89***	53	73	73	72
17	AFH-	***89***	50	72	72	71
18	ADI-	***89***	54	75	74	83
19	ADEI	***89***	55	75	73	83
20	AEF-	***89***	54	73	72	77
21	AEFH	***89***	54	73	73	73
22	BEFI	***88***	64	79	80	79
23	BEF-	***88***	66	79	79	84
24	BCEF	***88***	66	79	79	84
25	BFHI	***88***	62	78	77	83
26	BFH-	***88***	62	78	76	82
27	BFGH	***88***	62	78	76	82
28	BEFG	***88***	59	76	75	82
29	ABFI	***88***	56	75	73	81
30	BCFH	***88***	54	75	73	80
31	ABEI	***88***	51	72	71	81
32	ACD-	***88***	66	76	77	78
33	EFGI	***88***	53	74	74	77
34	ACDE	***88***	60	73	75	78
35	ACDF	***87***	53	71	73	71
36	EFHI	***87***	64	79	79	82
37	BCDF	***87***	51	72	72	77
38	AFHI	***87***	50	72	72	77
39	CDHI	***86***	54	76	74	75
40	BDEF	***86***	66	78	79	82
41	BEFH	***86***	64	76	77	81
42	ABF-	***86***	56	74	72	80
43	ABCF	***86***	56	74	72	80
44	ADHI	***86***	51	72	72	79
45	ABC-	***86***	53	70	70	78
46	AB--	***86***	50	69	69	78
47	FGHI	***86***	54	74	73	80
48	ADFI	***85***	58	75	74	82

49	DFHI	***85***	53	74	73	0
50	ABFH	***84***	59	74	73	78
51	ABEF	***84***	59	73	73	79
52	ABE-	***84***	57	71	71	78
53	ABCE	***84***	57	71	71	78
54	ABH-	***84***	53	69	69	76
55	ABCH	***84***	53	69	69	76
56	ABFG	***84***	52	70	70	76
57	ABG-	***84***	54	69	70	77
58	ABEG	***81***	57	69	70	76
59	ABEH	***81***	57	69	70	76
60	ABCG	***81***	52	66	69	74
61	DEHI	***77***	57	73	73	67

Table 2A (above) – Patient 2 to 11 Months of Age – Diagnostic Model Ordered According to Descending Sensitivity.

	Ordered according to descending specificity					
No	**Combination**	**SEN (%)**	***SPE (%)***	**ACC (%)**	**PPV (%)**	**NPV (%)**
1	ACDI	91	***70***	82	82	89
2	BEF-	88	***66***	79	79	84
3	BCEF	88	***66***	79	79	84
4	BDEF	86	***66***	78	79	82
5	ACD-	88	***66***	76	77	78
6	BEFI	88	***64***	79	80	79
7	EFHI	87	***64***	79	79	82
8	ACDH	89	***64***	77	78	74
9	BEFH	86	***64***	76	77	81
10	BFHI	88	***62***	78	77	83
11	BFH-	88	***62***	78	76	82
12	BFGH	88	***62***	78	76	82
13	ABCD	91	***61***	77	76	88
14	ACDE	88	***60***	73	75	78
15	BEFG	88	***59***	76	75	82
16	ABFH	84	***59***	74	73	78
17	ABEF	84	***59***	73	73	79
18	BFI-	91	***58***	78	75	86
19	BCFI	91	***58***	78	75	86
20	BFGI	91	***58***	78	75	86
21	ADFI	85	***58***	75	74	82
22	CEFI	89	***57***	77	76	81
23	DEHI	77	***57***	73	73	67
24	ABE-	84	***57***	71	71	78

25	ABCE	84	***57***	71	71	78
26	ABEG	81	***57***	69	70	76
27	ABEH	81	***57***	69	70	76
28	ABFI	88	***56***	75	73	81
29	ABF-	86	***56***	74	72	80
30	ABCF	86	***56***	74	72	80
31	CDEF	92	***56***	76	74	86
32	DEFI	89	***55***	76	74	81
33	ADEI	89	***55***	75	73	83
34	ABG-	84	***54***	69	70	77
35	AEF-	89	***54***	73	72	77
36	AEFH	89	***54***	73	73	73
37	EFI-	94	***54***	77	76	85
38	ADI-	89	***54***	75	74	83
39	CDHI	86	***54***	76	74	75
40	BCFH	88	***54***	75	73	80
41	FGHI	86	***54***	74	73	80
42	EFGI	88	***53***	74	74	77
43	DFHI	85	***53***	74	73	0
44	ACDG	89	***53***	73	73	72
45	ACDF	87	***53***	71	73	71
46	ABC-	86	***53***	70	70	78
47	ABH-	84	***53***	69	69	76
48	ABCH	84	***53***	69	69	76
49	ABFG	84	***52***	70	70	76
50	ABCG	81	***52***	66	69	74
51	CDF-	92	***52***	74	74	73
52	ADHI	86	***51***	72	72	79
53	BCDF	87	***51***	72	72	77
54	ABI-	91	***51***	73	72	85
55	ABCI	91	***51***	73	72	85
56	ABEI	88	***51***	72	71	81
57	CEF-	96	***50***	77	74	81
58	AFHI	87	***50***	72	72	77
59	AB--	86	***50***	69	69	78
60	ACFG	91	***50***	73	73	77
61	AFH-	89	***50***	72	72	71

Table 2B (above) – Patient 2 to 11 Months of Age – Diagnostic Model Ordered According to Descending Specificity

	Ordered according to descending accuracy					
No	**Combination**	**SEN (%)**	**SPE (%)**	***ACC (%)***	**PPV (%)**	**NPV (%)**
1	ACDI	91	70	***82***	82	89

2	BEF-	88	66	***79***	79	84
3	BCEF	88	66	***79***	79	84
4	EFHI	87	64	***79***	79	82
5	BEFI	88	64	***79***	80	79
6	BFHI	88	62	***78***	77	83
7	BFI-	91	58	***78***	75	86
8	BCFI	91	58	***78***	75	86
9	BFGI	91	58	***78***	75	86
10	BDEF	86	66	***78***	79	82
11	BFH-	88	62	***78***	76	82
12	BFGH	88	62	***78***	76	82
13	CEF-	96	50	***77***	74	81
14	ABCD	91	61	***77***	76	88
15	ACDH	89	64	***77***	78	74
16	EFI-	94	54	***77***	76	85
17	CEFI	89	57	***77***	76	81
18	BEFH	86	64	***76***	77	81
19	BEFG	88	59	***76***	75	82
20	CDEF	92	56	***76***	74	86
21	ACD-	88	66	***76***	77	78
22	CDHI	86	54	***76***	74	75
23	DEFI	89	55	***76***	74	81
24	ADI-	89	54	***75***	74	83
25	ADFI	85	58	***75***	74	82
26	ABFI	88	56	***75***	73	81
27	ADEI	89	55	***75***	73	83
28	BCFH	88	54	***75***	73	80
29	FGHI	86	54	***74***	73	80
30	DFHI	85	53	***74***	73	0
31	CDF-	92	52	***74***	74	73
32	EFGI	88	53	***74***	74	77
33	ABFH	84	59	***74***	73	78
34	ABF-	86	56	***74***	72	80
35	ABCF	86	56	***74***	72	80
36	ABEF	84	59	***73***	73	79
37	ABI-	91	51	***73***	72	85
38	ABCI	91	51	***73***	72	85
39	ACFG	91	50	***73***	73	77
40	AEF-	89	54	***73***	72	77
41	ACDE	88	60	***73***	75	78
42	ACDG	89	53	***73***	73	72
43	DEHI	77	57	***73***	73	67
44	AEFH	89	54	***73***	73	73
45	ADHI	86	51	***72***	72	79

46	BCDF	87	51	***72***	72	77
47	AFHI	87	50	***72***	72	77
48	AFH-	89	50	***72***	72	71
49	ABEI	88	51	***72***	71	81
50	ACDF	87	53	***71***	73	71
51	ABE-	84	57	***71***	71	78
52	ABCE	84	57	***71***	71	78
53	ABC-	86	53	***70***	70	78
54	ABFG	84	52	***70***	70	76
55	ABEG	81	57	***69***	70	76
56	ABEH	81	57	***69***	70	76
57	ABH-	84	53	***69***	69	76
58	ABCH	84	53	***69***	69	76
59	AB--	86	50	***69***	69	78
60	ABG-	84	54	***69***	70	77
61	ABCG	81	52	***66***	69	74

Table 2C (above) – Patient 2 to 11 Months of Age – Diagnostic Model Ordered According to Descending Specificity.

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	Ordered according to descending sensitivity					
No	**Combination**	***SEN (%)***	**SPE (%)**	**ACC (%)**	**PPV (%)**	**NPV (%)**
1	BEF-	***94***	51	81	81	67
2	BFI-	***92***	51	79	80	71
3	BEFI	***92***	51	79	80	65
4	CDF-	***92***	55	81	82	65
5	CDFH	***92***	50	78	80	65
6	BCEF	***91***	51	79	81	64
7	BDEF	***91***	51	79	81	64
8	AD--	***91***	60	74	76	71
9	ADH-	***91***	60	74	76	71
10	AEF-	***90***	51	74	75	71
11	ACEF	***90***	51	74	75	71
12	CDEI	***89***	55	80	80	66
13	CDFI	***89***	53	79	80	63
14	CDFG	***89***	55	79	82	63
15	ADI-	***89***	62	74	78	71
16	ABCE	***89***	54	74	77	67
17	ABEG	***89***	53	75	77	67
18	ABEH	***89***	53	75	77	56
19	ADGI	***89***	62	74	78	71
20	ADHI	***89***	62	74	78	67

21	DFI-	***89***	54	76	76	67
22	ADFI	***89***	54	76	76	73
23	CEFI	***89***	50	79	79	59
24	DEFI	***89***	50	79	79	57
25	ACD-	***89***	66	78	81	66
26	BEFH	***89***	51	78	81	62
27	ACDH	***89***	72	79	82	70
28	AFHI	***89***	51	73	76	69
29	ABC-	***88***	53	71	77	60
30	ABF-	***88***	58	74	79	73
31	ABCD	***88***	63	77	82	74
32	BCDF	***88***	51	76	80	67
33	ABCG	***88***	55	73	78	60
34	ABCH	***88***	53	71	77	60
35	ABCF	***88***	61	76	80	73
36	ABFG	***88***	58	74	79	73
37	AH--	***88***	58	73	75	77
38	AF--	***88***	51	73	75	65
39	ADG-	***88***	56	71	74	69
40	AFH-	***88***	64	74	77	77
41	ADGH	***88***	62	74	77	71
42	ADFG	***88***	50	73	74	69
43	ADFH	***88***	51	73	75	71
44	BFGI	***88***	60	78	79	71
45	ABI-	***88***	75	77	83	76
46	CFHI	***88***	50	73	75	65
47	AI--	***88***	56	70	75	70
48	ACI-	***88***	54	70	74	74
49	AGI-	***88***	51	68	74	57
50	AFI-	***88***	64	73	78	76
51	ABFI	***88***	80	81	85	78
52	ABFH	***88***	51	71	76	74
53	ACDI	***88***	74	78	82	76
54	ACGI	***88***	51	68	74	57
55	ACFI	***88***	64	73	78	76
56	AFGI	***88***	64	73	78	76
57	AEFH	***88***	51	73	74	69
58	CFGI	***87***	58	76	77	69
59	FGHI	***87***	52	73	76	58
60	ABEI	***87***	60	76	79	63
61	AGHI	***87***	56	70	75	65
62	EFI-	***86***	58	81	83	55
63	EFGI	***86***	58	81	83	55
64	ACH-	***86***	58	71	75	71

65	ACF-	***86***	51	71	75	60
66	ACFH	***86***	64	73	77	73
67	ABCI	***86***	71	74	80	74
68	AEFG	***86***	52	73	76	63
69	ABDI	***86***	71	74	81	70
70	ABGI	***86***	66	73	79	70
71	ABGH	***86***	53	69	77	57
72	DFGI	***85***	57	75	77	64
73	AHI-	***85***	56	68	75	64
74	AEFI	***85***	61	75	80	61
75	ACHI	***85***	56	68	75	64
76	ACDE	***84***	60	75	81	52
77	EFHI	***84***	51	77	80	52
78	ACDG	***84***	72	76	83	65
79	ACDF	***84***	51	75	80	55
80	BFHI	***84***	60	75	79	67
81	AG--	***84***	60	70	75	69
82	ACG-	***84***	64	71	77	71
83	AGH-	***84***	64	71	77	71
84	AFG-	***84***	66	73	78	71
85	ACGH	***84***	66	73	78	71
86	ACFG	***84***	64	71	77	71
87	AFGH	***84***	64	71	77	71
88	ABHI	***83***	60	68	76	64
89	CDEF	***82***	51	73	76	56

Table 3A (above) – Patient 12 to 60 Months of Age – Diagnostic Model Ordered According to Descending Sensitivity.

	Ordered according to descending specificity					
No	Combination	SEN (%)	***SPE (%)***	ACC (%)	PPV (%)	NPV (%)
1	ABFI	88	***80***	81	85	78
2	ABI-	88	***75***	77	83	76
3	ACDI	88	***74***	78	82	76
4	ACDH	89	***72***	79	82	70
5	ACDG	84	***72***	76	83	65
6	ABCI	86	***71***	74	80	74
7	ABDI	86	***71***	74	81	70
8	ABGI	86	***66***	73	79	70
9	AFG-	84	***66***	73	78	71
10	ACGH	84	***66***	73	78	71
11	ACD-	89	***66***	78	81	66
12	AFH-	88	***64***	74	77	77

13	AFI-	88	***64***	73	78	76
14	ACFI	88	***64***	73	78	76
15	AFGI	88	***64***	73	78	76
16	ACFH	86	***64***	73	77	73
17	ACG-	84	***64***	71	77	71
18	AGH-	84	***64***	71	77	71
19	ACFG	84	***64***	71	77	71
20	AFGH	84	***64***	71	77	71
21	ABCD	88	***63***	77	82	74
22	ADI-	89	***62***	74	78	71
23	ADGI	89	***62***	74	78	71
24	ADHI	89	***62***	74	78	67
25	ADGH	88	***62***	74	77	71
26	AEFI	85	***61***	75	80	61
27	ABCF	88	***61***	76	80	73
28	AD--	91	***60***	74	76	71
29	ADH-	91	***60***	74	76	71
30	AG--	84	***60***	70	75	69
31	ABHI	83	***60***	68	76	64
32	BFGI	88	***60***	78	79	71
33	ABEI	87	***60***	76	79	63
34	ACDE	84	***60***	75	81	52
35	BFHI	84	***60***	75	79	67
36	ABF-	88	***58***	74	79	73
37	ABFG	88	***58***	74	79	73
38	CFGI	87	***58***	76	77	69
39	AH--	88	***58***	73	75	77
40	ACH-	86	***58***	71	75	71
41	EFI-	86	***58***	81	83	55
42	EFGI	86	***58***	81	83	55
43	DFGI	85	***57***	75	77	64
44	ADG-	88	***56***	71	74	69
45	AI--	88	***56***	70	75	70
46	AGHI	87	***56***	70	75	65
47	AHI-	85	***56***	68	75	64
48	ACHI	85	***56***	68	75	64
49	CDF-	92	***55***	81	82	65
50	CDEI	89	***55***	80	80	66
51	CDFG	89	***55***	79	82	63
52	ABCG	88	***55***	73	78	60
53	ABCE	89	***54***	74	77	67
54	DFI-	89	***54***	76	76	67
55	ADFI	89	***54***	76	76	73
56	ACI-	88	***54***	70	74	74

57	CDFI	89	***53***	79	80	63
58	ABEG	89	***53***	75	77	67
59	ABEH	89	***53***	75	77	56
60	ABC-	88	***53***	71	77	60
61	ABCH	88	***53***	71	77	60
62	ABGH	86	***53***	69	77	57
63	AEFG	86	***52***	73	76	63
64	FGHI	87	***52***	73	76	58
65	AEF-	90	***51***	74	75	71
66	ACEF	90	***51***	74	75	71
67	AFHI	89	***51***	73	76	69
68	AF--	88	***51***	73	75	65
69	ADFH	88	***51***	73	75	71
70	AGI-	88	***51***	68	74	57
71	ABFH	88	***51***	71	76	74
72	ACGI	88	***51***	68	74	57
73	AEFH	88	***51***	73	74	69
74	ACF-	86	***51***	71	75	60
75	BEF-	94	***51***	81	81	67
76	BFI-	92	***51***	79	80	71
77	BEFI	92	***51***	79	80	65
78	BCEF	91	***51***	79	81	64
79	BDEF	91	***51***	79	81	64
80	BEFH	89	***51***	78	81	62
81	BCDF	88	***51***	76	80	67
82	ACDF	84	***51***	75	80	55
83	CDEF	82	***51***	73	76	56
84	EFHI	84	***51***	77	80	52
85	CDFH	92	***50***	78	80	65
86	CFHI	88	***50***	73	75	65
87	CEFI	89	***50***	79	79	59
88	DEFI	89	***50***	79	79	57
89	ADFG	88	***50***	73	74	69

Table 3B (above) – Patient 12 to 60 Months of Age – Diagnostic Model Ordered According to Descending Specificity.

	Ordered according to descending accuracy					
No	**Combination**	**SEN (%)**	**SPE (%)**	***ACC (%)***	**PPV (%)**	**NPV (%)**
1	EFI-	86	58	***81***	83	55
2	EFGI	86	58	***81***	83	55
3	BEF-	94	51	***81***	81	67
4	CDF-	92	55	***81***	82	65

5	ABFI	88	80	***81***	85	78
6	CDEI	89	55	***80***	80	66
7	CEFI	89	50	***79***	79	59
8	DEFI	89	50	***79***	79	57
9	BFI-	92	51	***79***	80	71
10	BEFI	92	51	***79***	80	65
11	BCEF	91	51	***79***	81	64
12	BDEF	91	51	***79***	81	64
13	CDFI	89	53	***79***	80	63
14	CDFG	89	55	***79***	82	63
15	ACDH	89	72	***79***	82	70
16	CDFH	92	50	***78***	80	65
17	ACD-	89	66	***78***	81	66
18	BEFH	89	51	***78***	81	62
19	BFGI	88	60	***78***	79	71
20	ACDI	88	74	***78***	82	76
21	ABCD	88	63	***77***	82	74
22	ABI-	88	75	***77***	83	76
23	EFHI	84	51	***77***	80	52
24	BCDF	88	51	***76***	80	67
25	ABEI	87	60	***76***	79	63
26	ACDG	84	72	***76***	83	65
27	DFI-	89	54	***76***	76	67
28	ADFI	89	54	***76***	76	73
29	ABCF	88	61	***76***	80	73
30	CFGI	87	58	***76***	77	69
31	ABEG	89	53	***75***	77	67
32	ABEH	89	53	***75***	77	56
33	DFGI	85	57	***75***	77	64
34	AEFI	85	61	***75***	80	61
35	ACDE	84	60	***75***	81	52
36	ACDF	84	51	***75***	80	55
37	BFHI	84	60	***75***	79	67
38	AD--	91	60	***74***	76	71
39	ADH-	91	60	***74***	76	71
40	AEF-	90	51	***74***	75	71
41	ACEF	90	51	***74***	75	71
42	ADI-	89	62	***74***	78	71
43	ABCE	89	54	***74***	77	67
44	ADGI	89	62	***74***	78	71
45	ADHI	89	62	***74***	78	67
46	ABF-	88	58	***74***	79	73
47	ABFG	88	58	***74***	79	73
48	AFH-	88	64	***74***	77	77

49	ADGH	88	62	***74***	77	71
50	ABCI	86	71	***74***	80	74
51	ABDI	86	71	***74***	81	70
52	CFHI	88	50	***73***	75	65
53	FGHI	87	52	***73***	76	58
54	CDEF	82	51	***73***	76	56
55	AFHI	89	51	***73***	76	69
56	AH--	88	58	***73***	75	77
57	AF--	88	51	***73***	75	65
58	ADFG	88	50	***73***	74	69
59	ADFH	88	51	***73***	75	71
60	AFI-	88	64	***73***	78	76
61	ACFI	88	64	***73***	78	76
62	AFGI	88	64	***73***	78	76
63	AEFH	88	51	***73***	74	69
64	ACFH	86	64	***73***	77	73
65	AEFG	86	52	***73***	76	63
66	ABGI	86	66	***73***	79	70
67	AFG-	84	66	***73***	78	71
68	ACGH	84	66	***73***	78	71
69	ABCG	88	55	***73***	78	60
70	ADG-	88	56	***71***	74	69
71	ABFH	88	51	***71***	76	74
72	ACH-	86	58	***71***	75	71
73	ACF-	86	51	***71***	75	60
74	ACG-	84	64	***71***	77	71
75	AGH-	84	64	***71***	77	71
76	ACFG	84	64	***71***	77	71
77	AFGH	84	64	***71***	77	71
78	ABC-	88	53	***71***	77	60
79	ABCH	88	53	***71***	77	60
80	AI--	88	56	***70***	75	70
81	ACI-	88	54	***70***	74	74
82	AGHI	87	56	***70***	75	65
83	AG--	84	60	***70***	75	69
84	ABGH	86	53	***69***	77	57
85	AGI-	88	51	***68***	74	57
86	ACGI	88	51	***68***	74	57
87	AHI-	85	56	***68***	75	64
88	ACHI	85	56	***68***	75	64
89	ABHI	83	60	***68***	76	64

Table 3C (above) – Patient 12 to 60 Months of Age – Diagnostic Model Ordered According to Descending Accuracy.

It will be noted in the above tables that a maximum of four diagnostic parameters are used in combination. This is because the Inventors research has surprisingly indicated that using a combination of more than four diagnostic features increases computational complexity without any substantial diagnostic performance gain.

If the clinician picks "accuracy" optimization then the best model will be the top row of Table A3 (if the patient is 2 to 11 months of age) and top Row of Table B3 (if the patient is 12 to 60 months of age). However, if the parameters that were entered by the clinician do not allow for the top row #1 to be used then the microprocessor will check if row #2 can be used and so on. Since the parameters that are listed (among the nine set out in table 1B) are common measurements usually it is not necessary to descend far down the rows to find a first usable model.

For example,

Table 2B: 2-11 months: parameters:

#1 ACDI (breathing rate, runny nose, #days with runny nose, oxygen saturation) >> Sens 91%, spec 70%.
#13 ABCD (breathing rate, fever, runny nose, #days with runny nose) >> sens 91%, spec 61% etc.

The flowchart of Figure 8 details the model selection process that microprocessor 3 performs under control of diagnostic application 6, within box 43 of the flowchart of Figure 2. Using the data for tables A1-A3 or B1-B3 (depending on age), the clinician's inputted preference for optimization for sensitivity, specificity or accuracy, and the inputted patient parameters, the device 1 automatically selects a particular numbered diagnostic model using the procedure set out in Figure 9.

At box 45 (Fig. 2) the patient values that were entered for each of the diagnostic parameters that were selected are applied by microprocessor 3 to the selected optimal diagnostic model. The screen that is depicted in Figure 10 is presented on LCD touchscreen interface 11 whilst this process runs.

At box 47 microprocessor 3 operating under control of the diagnostic application 6 operates the LCD touchscreen interface 11 to present the diagnostic results to the carer as shown in the screen of Figure 11.

Returning to the flowchart of Figure 2, at box 49 the microprocessor 3 may save the diagnosis results either locally to memory 5 or externally via WAN/WLAN interface and antenna 29 to cloud server 33 via data network 31. At box 50, if the diagnostic results indicate a disease state such as pneumonia then the carer may use that information, as indicated in box 52, to apply therapy to the patient 2, for example by organising hospitalisation and/or providing antibiotics or antiviral medication. The clinician 4 may then indicate, at box 55, a desire to diagnose another patient in which case the procedure is repeated in respect of another patient.

As will be explained in the Appendices of this specification, the Inventors developed the diagnostic models from quantitative test data derived from a population of subjects including patients suffering from respiratory disease. The various models are arranged to classify a patient as “diseased” or “non-diseased” based upon the diagnostic parameters for the patient that are entered by the clinician. A preferred approach to developing the models is by use of a logistic regression machine (LRM). Other types of classification decision engines may also be used, for example support vector machines (SVMs).

As explained in Section 1.2.2 of Appendix A herein, the use of cough sound features from just one or two coughs of a patient has been found by the Inventors to provide a significant diagnosis performance gain. Where it is possible to record a cough sound from patient 2 by means of microphone 25, those sounds can be processed by a cough feature extraction and processed

along with other diagnostic parameters by a suitable one of the diagnostic models 20.

Referring now to Figure 11A, there is shown a further embodiment of the invention comprising diagnostic device 1a, which as far as hardware is concerned is the same as previously described diagnostic device 1, programmed with a variation of the diagnostic application 6 that was previously discussed being diagnostic application 6a. Diagnostic application 6a includes a cough feature extraction engine 24. The cough feature extraction engine 24 includes instructions for the microprocessor 3 to analyse a cough sound from the patient 2 that is received via microphone 25 and audio interface 21 and to generate corresponding cough features. Cough feature extraction is known in the prior art and is described for example in international patent publication No. WO 2013/142908 by present Inventor Abeyratne et al., the disclosure of which is hereby incorporated by reference in its entirety.

Microprocessor 3 applies the cough features to diagnostic models 20 that form part of the diagnostic application 6a and which are configured to take into account other diagnostic parameter values that are input by the clinician 4. This is done by adding cough features as a grouped-features to the existing lookup tables set out as Tables 2A – 3C. The modified tables including the cough sounds are arranged with the models in decreasing performance as before. Users, e.g. clinician 4, can select the cough sounds as a measurement in the event that they are able to collect sounds from patient 2. Otherwise they do not elect that option, just as in the case of other clinical signs. Then following the same logic as discussed previously with respect to Tables 2A-3C the diagnostic device 1 is programmed by means of diagnostic application 6 to pick the best model corresponding to the available measurements.

Figures 11B and 11C depict screens 54, 56 that are generated on LCD touchscreen interface 11 by the microprocessor 3 under control of the diagnostic application 6 to prompt for the clinician 4 to capture at least two cough sound samples from the patient 2. Figure 11D depicts a screen 57 that the microprocessor 3 generates on interface 11 for presenting the results of

the analysis to the clinician 4. As discussed in Appendix A, in other embodiments only a single cough sound has been found to assist in improving the performance of the machine diagnosis.

APPENDIX A

Childhood Pneumonia Diagnosis Using Clinical and Cough Features

1.1 Materials and method

1.1.1 Study population

A total of 222 children were recruited during the data collection: 93 females and 129 males with a median age of 9 months and an inter-quartile range (IQR) of 4.25-20 months. Due to the absence of one or more of the required parameters, we excluded 123 patients from further consideration, leaving 99 children with complete data. The distribution of the 99 children is a close representation of the initial 222 children recruited, as shown in Table 4.1. There were 52 children aged 2-11 months and 47 aged 12-60 months. Of the 99 children, 67 were pneumonia positive, whereas the remaining 32 experienced a mix of asthma, bronchitis, bronchiolitis, heart disease, malnutrition, wheezing, etc. The non-pneumonia patients are the control set for this study.

Table 4.1 Children representation between initial recruitment and actual number in study

Category	**Initial Recruitment (n=222)**	**Model Building (n=99)**
Age		
- Median	10 months	11 months
- IQR	17 months	6 months
Diagnosis Ratio	2.47:1	2.1:1
- Pneumonia	158 patients	67 patients
- Non-Pneumonia	64 patients	32 patients

Gender Ratio (M/F)	1.39:1	1.3:1
- Male	128 patients	56 patients
- Female	92 patients	43 patients
Age Group		
- <2 Months	13 subjects	0 subjects
- 2-11 Months	109 subjects	52 subjects
- 12-60 Months	100 subjects	47 subjects

1.1.2 Analysis of data

The flow diagram 1200 presented in Figure 12 details the process used in analysing our data. For analysis, the dataset is split into two age groups, 2-11 months and 12-60 months. This follows the WHO/IMCI procedure which applies different breathing rate thresholds for each age group. Clinical and cough features from each group are tabled into a feature matrix for processing.

An LRM classifier was used to train a model for each feature combination. This technique creates a non-linear model based on the feature parameters and applies different weights to each parameter. The LRM training process adjusts the weights such that each model is adapted to differentiate pneumonia patients from non-pneumonia patients. We exhaustively analysed feature combinations from one up to six features at a time. The process was divided into several phases: clinical features only, clinical plus cough features from one cough, and clinical plus cough features from two coughs. Cough features from multiple coughs were averaged to a single set prior to analysis.

Leave one out (LOO) cross-validation was used to validate the results. At each iteration, one patient was designated the LOO person and the rest became training set. An LRM model was created based on the training set and the cut-off threshold, carefully selected such that Sn ≥ 90% with Sp as high as possible. The model parameters were then fixed and used to evaluate the training set and LOO individual. Applying the trained model on the training set provides the training performance such that the LOO person is classified using

the trained model. On the next iteration, another individual is designated LOO whilst the others become the training set. At the end of the iteration process where every patient has been designated once as an LOO individual, the procedure performance was calculated.

1.2 Results

In this section, we show the results of our analysis in three phases. Firstly, we compare the WHO/IMCI procedure performance in each age group with clinical features only. This is followed by comparison with clinical features plus features from one cough. Lastly, we compare the WHO/IMCI procedure results with our procedure using clinical plus cough features from two coughs.

1.2.1 Clinical only features

The results in Table 4.2 show the WHO/IMCI classification and our procedure performance using only clinical features for each age group. The WHO/IMCI procedure performed with an Sn and Sp of 91.2% and 26.7%, respectively, for the 2-11 month age group. In the older age group, the corresponding Sn and Sp are 83.3% and 11.8%. The best model in the 2-11 month age group, using clinical features only, demonstrated an Sn and Sp of 86.5% and 60.0%, respectively, using fever, days with cough, temperature and heart rate. In the 12-60 month age group, the best model identified used fever, temperature, runny nose and heart rate, with an Sn and Sp of 90.0% and 76.6%, accordingly.

1.2.2 Clinical plus one cough

When features from just one cough were added to the mix, there was significant performance gain. For the 2-11 month age group, the best model showed an Sn and Sp of 89.2% & 73.3%, respectively. This Sp value is the equivalent of 275% that of the WHO/IMCI procedure with only a small drop in the Sn. The numbers can be seen in Table 4.3. For the 12-60 month age group, the best model using clinical features and one cough performed with an Sn and Sp of 90.0% & 82.4%, respectively. Compared to the WHO/IMCI

performance, the Sp is equivalent to 82.4/11.8 = 698% and the Sn is slightly higher than the WHO/IMCI's.

Table 4.2 Performance comparison between WHO and clinical feature combinations

Classification Performance (%)					
2-11 Months	***Sn***	***Sp***	***Acc***	**PPV**	**NPV**
WHO	91.2	26.7	73.1	75.6	57.1
Fever + Days with cough + Temperature + Heart rate					
Training	91.7	64.9	84.0	86.6	76.0
LOO	86.5	60.0	78.8	84.2	64.3
Days with cough + Breathing rate + Temperature + Days with runny nose					
Training	91.9	60.2	82.8	85.1	75.0
LOO	86.5	53.3	76.9	82.1	61.5
Fever + Days with cough + Runny nose + Heart rate					
Training	92.3	33.8	75.4	77.5	64.0
LOO	89.2	33.3	73.1	76.7	55.6
12-60 Months	***Sn***	***Sp***	***Acc***	**PPV**	**NPV**
WHO	83.3	11.8	57.5	62.5	28.6
Fever + Temperature + Runny nose + Heart rate					
Training	92.0	67.9	83.2	83.5	82.8
LOO	90.0	70.6	83.0	84.4	80.0
Fever + Days with cough + Temperature + Heart rate					
Training	92.1	68.5	83.5	83.8	83.0
LOO	86.7	70.6	80.9	83.9	75.0
Breathing rate + Temperature + Runny nose + Days with runny nose					
Training	92.1	51.3	77.2	77.3	77.7
LOO	86.7	70.6	80.9	83.9	75.0

*LOO = leave one out, Sn = sensitivity, Sp = Specificity, Acc = accuracy, PPV = positive predictive value, NPV = negative predictive value

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Table 4.3 Performance comparison between WHO and clinical plus one cough feature combinations

Classification Performance (%)					
2-11 Months	S_n	S_p	A_{cc}	**PPV**	**NPV**
WHO	91.2	26.7	73.1	75.6	57.1
Days with cough + Temperature + Days with runny nose + 1 cough					
Training	91.7	79.7	88.3	91.8	79.6
LOO	89.2	73.3	84.6	89.2	73.3
Fever + Days with cough + 1 cough					
Training	91.7	66.7	84.5	87.2	76.6
LOO	89.2	66.7	82.7	86.8	71.4
Days with cough + Breathing rate + Temperature + 1 cough					
Training	92.1	61.4	83.2	85.5	75.8
LOO	89.2	60.0	80.8	84.6	69.2
12-60 Months	S_n	S_p	A_{cc}	**PPV**	**NPV**
WHO	83.3	11.8	57.5	62.5	28.6
Temperature + Runny nose + Heart rate + 1 cough					
Training	92.0	82.2	88.4	90.1	85.3
LOO	90.0	82.4	87.2	90.0	82.4
Breathing rate + Days with runny nose + 1 cough					
Training	92.0	64.7	82.0	82.6	81.8
LOO	86.7	82.4	85.1	89.7	77.8
Fever + Runny nose + 1 cough					
Training	92.1	43.3	74.4	74.3	75.6
LOO	90.0	52.9	76.6	77.1	75.0

*LOO = leave one out, Sn = sensitivity, Sp = specificity, Acc = accuracy,

PPV = positive predictive value, NPV = negative predictive value

Table 4.4 Performance comparison between WHO and clinical plus two coughs feature combinations

Classification Performance (%)					
2-11 Months	S_n	S_p	A_{cc}	**PPV**	**NPV**
WHO	91.2	26.7	73.1	75.6	57.1
Days with cough + Breathing rate + Temperature + 2 coughs					
Training	91.8	85.7	90.0	94.1	80.9

LOO	89.2	86.7	88.5	94.3	76.5
Days with cough + 2 coughs					
Training	91.7	80.5	88.5	92.1	79.8
LOO	89.2	80.0	86.5	91.7	75.0
Fever + Days with cough + Breathing rate + Days with runny nose + 2 coughs					
Training	91.7	86.4	90.2	94.3	80.9
LOO	86.5	80.0	84.6	91.4	70.6
12-60 Months	S_n	S_p	A_{cc}	**PPV**	**NPV**
WHO	83.3	11.8	57.5	62.5	28.6
Breathing rate + Temperature + Heart rate + 2 coughs					
Training	92.1	83.7	89.0	90.9	85.7
LOO	90.0	88.2	89.4	93.1	83.3
Fever + Runny nose + O2 Saturation + 2 coughs					
Training	92.0	74.5	85.6	86.5	84.1
LOO	90.0	76.5	85.1	87.1	81.3
Fever + Runny nose + BMI + 2 coughs					
Training	92.1	69.4	83.8	84.3	83.4
LOO	90.0	70.6	83.0	84.4	80.0

*LOO = leave one out, Sn = sensitivity, Sp = specificity, Acc = accuracy,

PPV = positive predictive value, NPV = negative predictive value

1.2.3 Clinical plus two coughs

Table 4.4 shows the LRM performance when clinical features are combined with features from two coughs. The best model for the 2-11 month age group utilises days with cough, breathing rate and temperature along with the cough features. This results in Sn and Sp of 89.2% and 86.7%, respectively. The Sp is equivalent to 325% that of the WHO/IMCI procedure. In the 12-60 month age group, the best LRM model uses breathing rate, temperature and heart rate along with cough features. The model performance was 90.0% Sn and 88.2% Sp. The Sp in this case is equivalent to 747% of the WHO/IMCI counterpart.

1.3 Discussion

The aim in this study was to investigate the use of common clinical parameters in conjunction with cough sound analysis to diagnose childhood pneumonia. A key requirement for this objective is to perform better than the WHO/IMCI procedure. Our results have shown that adding cough sound analysis indeed helps identify childhood pneumonia better than just relying on clinical parameters. In this study, the WHO/IMCI procedure performed with an Sn and Sp range of 83-91% and 12-27%, respectively. Our best performing models with two cough sounds were able to classify pneumonia with an Sn and Sp range of 89-90% and 87-88%, respectively. These are the results from the LOO validation.

Cough is one of the most common symptoms in children with respiratory problems. The WHO/IMCI procedure takes into account the existence of cough but does not utilise it fully. Our method extracts the important features from cough sound recordings and uses them to augment our clinically based features in diagnosing pneumonia. We have shown this to provide the best performance compared to using cough sounds or clinical features only.

The field of cough sound analysis is still relatively untouched, despite the recent advancement in technology. We believe cough contains much more information regarding the physiology of the lung compared to what is currently known. A diseased lung hypothetically could change the physical characteristics of the lung and the characteristic sound of cough in a way specific to the disease. In the case of childhood pneumonia, we have shown in our previous studies that cough is a feasible parameter to use for diagnosis [7, 62]. The number of coughs used there was 15 per person, much higher that what has been used in this thesis. We now have shown that, combined with clinical parameters, much fewer cough sounds are potentially required in order to produce an accurate diagnosis.

1.4 Conclusion

We have demonstrated the potential benefits of combining clinical and cough features for childhood pneumonia diagnosis in resource-poor regions. The models we developed exhibited sensitivities of ~90% and specificities in the

range of 325-747% times the WHO/IMCI procedure. The key parameters that worked best were the combination of breathing rate, temperature, heart rate and cough sound analysis. The clinical features are easily measurable and in the absence of key parameters, we could switch to other models and they can still perform well.

It should be noted that this study is currently based on a relatively small number of subjects (n = 99) and there is yet to be established a gold standard for pneumonia diagnosis. The reference standard we used stems from a combination of clinical diagnosis by paediatricians aided by auscultations, laboratory analysis, chest x-ray (where applicable) and the subject's response to treatment over the clinical course of the disease.

----------End of Appendix A----------

APPENDIX B

Exhaustive Mathematical Analysis of Simple Clinical Measurements

In 1990, the World Health Organization (WHO) and UNICEF proposed the WHO criteria for childhood pneumonia classification in resource-poor regions. This is the current de facto diagnostic method used by community health workers in resource limited settings as a rapid low cost alternative in frontline health facilities. Table 5 shows the WHO/IMCI guideline for pneumonia classification in resource poor regions.

Table 5 – WHO/IMCI guidelines for pneumonia classification in resource-poor regions [35,36]

Sequence for Criteria Application	Classification
1.History of cough and/or difficult breathing of less than 3 weeks duration	Screened in for next procedure
2.Increased respiratory rate (tachypnea): ≥60/min if age <2 months, ≥50/min if age 2-11 months, ≥40/min if age 12-60 months	Non-severe pneumonia
3.Lower chest wall indrawing	Severe pneumonia
4.Cyanosis or inability to feed or drink	Very severe pneumonia

The WHO/IMCI guideline dictates that if a patient exhibits symptoms of cough/breathing difficulty, the patient is screened for the next step.

Breathing rate is taken and if it exceeds the limit (50 breaths per minute (bpm) for age 2-11 months, 40 bpm for age 12-60 months), non-severe pneumonia is declared. Danger signs such as lower chest indrawing and inability to feed or drink would put the patient in the severe pneumonia category requiring immediate attention.

Researchers have generally recognized the limitations of the WHO criteria, which are sensitive but not very specific [9, 15, 16]. Over the years, others have suggested the addition of fever [17], grunting and nasal flaring [8], temperature and oxygen saturation [18]. Rambaud-Althaus et al. proposed a combination of signs in a decision tree format to improve clinical diagnosis accuracy [8]. Pneumonia Etiology Research for Child Health (PERCH) investigators developed their own standard interpretations of the symptoms and signs based on the WHO criteria for a clinical case definition of pneumonia [16].

All these approaches make important contributions to dealing with the global burden of pneumonia, but largely suffer from the same type of limitations afflicting the WHO criteria for resource-poor regions. These methods also rely on health workers to perform measurements and interpret data using basic binary decisions around fixed thresholds.

METHODS

Study organization

The clinical data used for this study were collected by the Gadjah Mada University-Sardjito Hospital, Yogyakarta, Indonesia, in partnership with The University of Queensland, Brisbane, Australia. The data collection began in December 2010 and continued until March 2014. The ethics committees of the Sardjito Hospital and The University of Queensland approved the study protocol. The inclusion/exclusion criteria are given in Table 6 (Supplementary) below:

Table 6 – Patient Recruitment Criteria

Inclusion criteria	Exclusion criteria
• Patients with symptoms of chest infection.	• Advanced disease where recovery is not expected e.g.
• At least 2 of:	• Terminal lung cancer
○ Cough	• Droplet precautions
○ Sputum	• NIV required
○ Increased breathlessness	
○ Temperature >37.5°C	
• Consent from parent/guardian	• No informed-consent

Patients are included if they exhibit any 2 symptoms of cough, sputum, increased breathlessness and temperature >37.5°C. Parental consent was sought prior to inclusion if the patient met the criteria and excluded if consent was not granted. Exclusion criteria also applied to patients showing symptoms of advanced disease, terminal lung cancer and/or requiring a nasal drip IV, as these may skew the outcomes. As a precaution, patients showing droplet-spread disease were also excluded.

Diagnostic definitions

The reference diagnosis used in this study is the overall diagnosis provided by the pediatricians on the basis of clinical presentation, laboratory tests, chest X-ray, and the clinical course of the disease. An X-ray was performed only on subjects clinically suspected of pneumonia and, on other occasions, where there is clear need for it.

Therefore, not all our subjects underwent a chest X-ray.

Study protocol

All children who satisfied the inclusion criteria were invited to participate in the study. Each child's history and clinical measurements were recorded as part of the hospital admission process. Diagnostic outcomes and all test results collected from the subjects in the course of normal diagnosis/management of the disease were made available to this study. Table 7 (Supplementary) lists some of the information recorded which was used for analysis in this paper.

Table 7 – List of clinical parameters recorded at the time of admission

History	Recorded details	Examination	Recorded details
Fever	Yes/No	Age	Months
Days with fever	Days	Weight	Kg
Cough	Yes/No	Height	m
Days with cough	Days	Breathing rate	Breaths/min
Runny nose	Yes/No	Heart rate	Beats/min
Days with runny nose	Days	Temperature	°C
Breathing difficulty	Yes/No	BMI	Number
Days with breathing difficulty	Days	Oxygen saturation	Percentage
		Chest indrawing	Yes/No

The test parameters included the existence of fever, cough, breathing difficulty, runny nose, and chest indrawing as a binary yes/no observation. It also included the following data as numbers: age, weight, height, breathing rate, temperature, BMI, oxygen saturation, and number of days suffering fever, cough, breathing difficulty, runny nose. Other diagnostic measures such as blood/sputum analysis and chest X-ray were performed only if the attending physician deemed it to be necessary.

Study population

We recruited 222 children in total: 93 females, 129 males with a median age of 9 months and an inter-quartile range (IQR) of 4.25-20 months. Our population came from subjects admitted to the hospital ward. Our intention was to focus on the clinical parameters of interest in diagnosing pneumonia in resource poor regions. The dataset comprised 134 children with the complete list of parameters specified earlier. We excluded 88 patients from further consideration due to the absence of one or more of the required parameters. The distribution of the chosen 134 children closely represented the initial 222 children recruited, as shown in Table 8.

Table 8 – Children representation between initial recruitment and actual number in study

Category	Initial Recruitment (n=222)	Model Building (n=134)
Age		
- Median	10 months	11 months
- IQR	17 months	21 months
Diagnosis Ratio	2.47:1	2.62:1
- Pneumonia	158 patients	96 patients
- Non-Pneumonia	64 patients	38 patients
Gender Ratio (M/F)	1.39:1	1.27:1
- Male	128 patients	75 patients
- Female	92 patients	59 patients
Age Group		
- <2 Months	13 subjects	0 subjects
- 2-11 Months	109 subjects	71 subjects
- 12-60 Months	100 subjects	63 subjects

There were 71 and 63 children in the age groups 2-11 months and 12-60 months, respectively. Of the 134 children, 96 were diagnosed with pneumonia, whereas the remaining 38 were a mix of asthma, bronchitis, bronchiolitis, heart disease, malnutrition, wheezing, etc.

The non-pneumonia group served as the control set for this study.

Analysis of data

The flow diagram 1300 presented in Figure 13 details the process used in analysing our data. The data set is split into two age groups, 2-11 months and 12-60 months.

Clinical features from each group are tabled into a feature matrix for processing.

Using a *k*-fold cross validation method, each age group was randomly split into *k* number of folds. An iterative process was then adopted in which one fold of data was retained as the testing set whilst the rest of the data was used for training a logistic regression model (LRM). A good general explanation of the logistic regression method used in medical applications can be found in a paper by K.L. Sainani [26].

The LRM outputs the probability of the existence of pneumonia based on the specified predictors, to which a cut-off threshold is applied to make the output a binary decision. This threshold was carefully selected following a receiver operating characteristic (ROC) analysis to separate the positive and negative pneumonia cases as cleanly as possible.

In the LRM design, we commenced by using one feature at a time and computing the performance of the resulting models. We then exhaustively searched all combinations of two features taken at a time. This process was continued until we reached all 17 features taken at a time. In each iteration, the trained models were evaluated according to their sensitivity (S_n), specificity (S_p), accuracy (A_{cc}), and the area under the curve (AUC). AUC was only available for the training data to set the diagnostics threshold.

Note that in each fold of the k-fold cross validation, the data set was divided into non-overlapping training and testing sets, and the performance was estimated separately for both the training and testing sets. Each iteration generated k number of ROC curves and k sets of training and testing performance measures. Each iteration also generated k number of trained LRM models. The trained LRM models were used to calculate the performance of the training set. The LRM models were then fixed, and used on the testing data set to compute the testing performance and validate the trained model. Each set of LRM models was considered final for its respective fold. Hence, for testing performance, no AUC data were available.

The best performing models were chosen based on the means and standard deviations (SD) of the training and testing performances. These numbers were calculated and are reported in the Results section. Similarly, the WHO criteria performance numbers were calculated for the testing sets and represented using their means and SDs. We then used the performance values to determine which parameters, in which combinations could provide the best diagnostic outcomes with the testing sets.

This process was iterated for each feature combination used. First we analyzed the LRM performance of using one, two, and three features at a time. Next, we exhaustively analyzed all possible feature combinations with up to 17 features being used at once. Table 9 shows the possible combinations for each number of features used in the creation of the LRM model.

Table 9 – Total number of feature combinations possible out of 17 features available.

No of Features	No of possible Combinations
1	17
2	136
3	680
4	2,380
5	6,188
6	12,376
7	19,448
8	24,310
9	24,310
10	19,448
11	12,376
12	6,188
13	2,380
14	680
5	136
16	17
17	1
Total	131,071

Using one feature at a time gives 17 possible combinations, whereas using all 17 features at a time would have only one possible combination. The number of possible combinations rises significantly in between. For example, the use of 8 features at a time results in 24,310 combinations. In total, the number of models tested in this study is comprised of 131,071 combinations. Given the large number of models tested, the ROC curve analysis to find the best cut-off threshold for each model becomes very important. We selected the threshold

targeting a $S_n \geq 90\%$ with S_p as high as possible. This also had the benefit of lowering the false discovery rate (FDR). As we mentioned earlier, our aim is to improve the S_p of the WHO procedure, while maintaining high S_n.

RESULTS

In this section, we show the results of our analysis, starting from the cross-validation process and the WHO/IMCI procedure performance in our patient groups. We then describe the performance of our models and compare with the WHO outcomes in the 2-11 month age group, followed by the 12-60 month age group.

The Cross-validation technique

As detailed in Methods section, we use *k*-fold cross-validation to train and evaluate our classifier models. In this study we set k=8, resulting in 8-9 children in each fold. Higher k values, such as the more commonly used k=10, would result in 6-7 children in each fold. We deemed this number as insufficient and decided k=8 gives better balance for the testing data. Note that in each fold of the cross validation, training and testing sets are mutually exclusive, that is training and test testing sets do not overlap.

WHO/IMCI performance

We applied the WHO criteria (see Table I) to data in each fold of the k-fold cross validation data set, and computed the mean and the standard deviation (SD) across all folds. Results are shown in Table 10.

Table 10 – WHO criteria as applied to k-fold testing sets (Expressed in mean +/- standard deviation)

Age Group		Classification Performance (%)				
		S_n	S_p	A_{cc}	PPV	NPV
2-11 mth	Mean	92.0	38.1	69.1	67.6	76.2
	SD	11.6	18.5	11.2	12.5	28.0
12-60 mth	Mean	95.7	9.8	66.5	66.5	60.0
	SD	7.6	13.1	12.8	15.2	49.0

As expected, WHO criteria yielded high S_n with relatively small SD across both age groups, but at a poor specificity S_p.

Our target is to maintain the high sensitivity of the WHO procedure while increasing the specificity. Next we describe the performance of the proposed method. As the analysis was done separately for each age group, we will begin by presenting the results for the 2-11 month age group.

Performance in the 2-11 month age group

Figures 14A to 14C show mean S_n and S_p values for models using one, two, and three features at a time for the 2-11 month age group. Our feature set consisted of 17 observations/measurements as listed in Table 11. The number of total combinations of one-feature taken at a time is 17, leading to 17 LRM models with one feature as the input (Fig. 14A). Similarly, two features at a time and three features at a time give us 136 and 680 LRM models respectively (Fig.14B and Fig 14C bottom frames). Overall, significant benefits were found in combining features up to four at a time in one LRM.

Figure 15 shows the ROC curve analysis for 12 trained LRM models we selected for further consideration. Two models each are from single and double feature combinations, five from triple feature combinations, and three with four feature combinations. The solid line in each frame represents the mean ROC curve, formed over the k folds. Crosses on each frame represent the SD of the S_n and 1- S_p at points shown. On each frame of Fig. 15, we also graphically illustrate (see boxes) the performance possible with the WHO/IMCI procedure for resource-limited regions. The centre of the box indicates the mean performance, and the height and width of the box represent SD. Table 11 shows the training and testing performance numbers for the 12 models.

Table 11 – Performance comparison between various models for diagnosing pneumonia in children aged 2-11 months (AUC=Area Under Curve, CO= Cut-Off threshold).

Features		Training Performance (%)					Testing Performance (%)		
		S_n	S_p	A_{cc}	AUC	CO	S_n	S_p	A_{cc}
Temperature	Mean	93.2	11.9	59.9	71.7	38.4	88.8	11.3	58.7
	SD	1.4	9.8	3.9	2.5	3.7	13	12.2	12.2
Breathing rate (BR)	Mean	93.5	35.4	69.8	74.9	35.6	91.3	35.2	65.7
	SD	1.5	12	4.3	2.2	2.5	13	29.8	17.1
Chest indrawing	Mean	97.6	34.4	71.8	66	67.9	97.9	32.9	71.6
	SD	1	3.4	1.6	1.8	1.8	5.9	23.7	10.7
Fever + Breathing rate	Mean	93.2	44.5	73.2	82.1	33.5	86	50.2	69.1
	SD	1.5	11.2	4.7	2.6	3.7	17.9	26.6	18.2
Oxygen(O2) saturation+ Breathing rate	Mean	91.8	37.9	69.8	75.0	37.2	91.2	35.2	65.7
	SD	0.3	11.6	5.0	2.3	3.4	13.0	29.8	17.0
Age (months) + Fever + Breathing rate	Mean	91.8	63.7	80.3	83.3	39.9	86	66.7	76.6
	SD	0.3	7.9	3.4	2.4	5.1	17.9	22.5	16.8
Age (months) + Fever + Days with cough	Mean	91.8	63.7	80.3	81.2	41.3	83.5	67.3	76.1
	SD	0.3	4.5	2.4	1.9	10.6	14.5	23.9	18.5
Fever + Temperature + Chest indrawing	Mean	91.8	62.1	79.7	82.6	46	90.6	57.7	77.8
	SD	0.3	1.2	0.8	1.8	5.6	13.7	13	10.6
Fever + O2 saturation + Chest indrawing	Mean	92.8	64	81.1	77.9	44.1	88.1	61.9	77.6
	SD	1.5	3	1.6	1.9	8.7	13.6	8.7	10.9
Fever + Breathing rate + Chest indrawing	Mean	91.8	59.2	78.5	83.6	41.4	86	56.3	73.6
	SD	0.3	4.7	2.2	2.1	4.3	17.9	10.1	14.1
Fever + Days with cough + Heart rate + Chest indrawing	Mean	92.2	65.9	81.5	84.7	59.6	86.0	63.5	76.3
	SD	1.0	6.5	2.6	2.6	7.9	15.5	18.6	13.3
Runny nose + Days with runny nose + BR + Temp	Mean	91.8	77.4	85.9	88.1	51.0	91.3	70.2	82.0
	SD	0.3	6.1	2.5	2.1	6.1	13.0	22.8	9.3
Runny nose + Days with runny nose + BR + Heart rate	Mean	91.8	64.0	80.5	83.5	41.5	91.5	66.0	80.1
	SD	0.3	4.6	2.0	2.2	2.6	9.2	26.3	12.1

When a single feature is used to create the LRM for the 2-11 month age group, the best features in terms of testing performance were breathing rate (S_n of 91% and S_p of 35%) and chest in-drawing (S_n of 98% and S_p of 33%). These numbers closely matched the performance of the WHO criteria, as it also relies on the same features for childhood pneumonia classification.

Individually, the breathing rate and temperature exhibit the highest AUC in the training performance. However, the temperature model shows high S_n and lower S_p compared to the WHO criteria, as opposed to breathing rate model which has comparable numbers. On the testing dataset, both models

demonstrate high S_n with little SD, but the SDs of the S_p vary wildly, rendering both models unusable by themselves. This suggests that the WHO criteria are still more reliable when compared to single feature LRM models.

The use of two features at a time boosts the S_p to 50% for certain feature combinations while maintaining S_n around 90%. This is a significant improvement from the S_p of the best single feature model. The best performers are models using breathing rate with oxygen saturation, and, breathing rate with fever. Both feature combinations exhibit high AUC (75-82%) in training.

We continued to add features further until the optimal LRM feature combinations were found. On the three simultaneous feature models, the overall testing performances are higher than the double feature ones. Mean S_n levels remain largely the same around 90% and mean S_p levels are on average 30% higher than the double feature models. The SD levels for S_n is unchanged but for S_p is 44% smaller. The best performing model for this category includes fever, oxygen saturation and chest in-drawing as parameters, achieving a S_n value of 88.1±13.6% and an S_p value of 61.9±8.7%. Compared to WHO/IMCI procedure (S_n and S_p of 92.0±11.6% and 38.1±18.5%, respectively), the mean S_n is 4% lower while S_p is 62% higher. The SDs are 17% larger for S_n and 53% smaller for S_p compared to WHO. Thus, the best triple feature model performs much better than WHO criteria in terms of S_p, with a small loss of S_n.

Further improvements in classification performance are found using four features at a time. The best performing model uses the existence of runny nose, number of days with runny nose, breathing rate and temperature (91.3±13.0% S_n and 70.2±22.80% S_p). The mean S_n is on a par with the WHO results, and the mean S_p is 84% higher. The SD for both S_n and S_p are, however, slightly higher compared to WHO/IMCI procedure. The second best performing model uses runny nose, days with runny nose, breathing rate, and heart rate at S_n of 91.5±9.2% and S_p of 66.0±26.3%. The mean S_n is also on a par with the WHO results while S_p is 73% higher. For SDs, they are 20% smaller for S_n and 42% larger for S_p compared to WHO.

Performance in the 12-60 month age group

For the 12-60 month age group, the same process is repeated, starting with observation of the ROC curves from 12 trained LRM models chosen for comparison, as shown in Fig. 16, which is a ROC curve analysis for the age group of 12-60 month. The solid line in each frame represents the mean ROC curve, formed over *k*-iterations. Crosses on each frame represent the SD of the S_n and 1- S_p at points shown. On each frame, the performance of WHO/IMCI procedure for resource-limited regions is graphically illustrated by the crossed boxes. The center of the box indicates the mean performance, and the height and width of the box represent SD.

Table 12 – Performance comparison between trained models and WHO criteria for children aged 12-60 months (AUC=Area Under Curve, CO= Cut-Off threshold).

Features		Training Performance (%)					Testing Performance (%)		
		S_n	S_p	A_{cc}	AUC	CO	S_n	S_{pA}	A_{cc}
Temperature	Mean	93.0	10.7	64.4	70.4	46.6	88.0	19.2	61.6
	SD	1.6	13.6	3.9	2.6	3.2	14.0	35.0	35.0
Breathing rate (BR)	Mean	93.0	41.5	75.1	74.9	42.6	88.2	45.2	71.2
	SD	1.6	9.4	2.9	2.8	4.2	14.6	32.0	15.2
Chest indrawing	Mean	97.6	32.0	74.6	64.8	72.3	97.5	32.3	74.3
	SD	1.0	4.9	3.0	2.5	3.0	7.1	35.8	20.6
Fever + Breathing rate	Mean	92.0	49.6	77.3	82.0	41.4	88.3	44.2	67.9
	SD	1.1	10.5	3.1	2.4	5.9	15.2	47.7	21.1
Oxygen(O2) saturation+ Breathing rate	Mean	91.6	47.0	76.0	79.3	46.5	88.2	57.7	72.2
	SD	0.4	6.5	3.2	2.7	6.5	14.6	31.3	17.5
Age (months) + Fever + Breathing rate	Mean	91.6	58.4	80.0	81.5	46.9	88.3	70.6	75.9
	SD	0.4	10.3	3.6	2.5	7.2	15.2	33.5	14.9
Age (months) + Fever + Days with cough	Mean	91.6	60.4	80.7	79.3	53.5	84.3	59.6	74.6
	SD	0.4	4.3	2.0	2.2	9.4	21.2	37.6	13.4
Fever + Temperature + Chest indrawing	Mean	92.0	57.7	80.0	80.6	51.8	92.1	51.3	79.2
	SD	0.9	3.8	1.4	2.6	9.7	15.8	39.0	16.5
Fever + Breathing rate + Chest indrawing	Mean	91.6	66.4	79.4	82.3	49.0	88.3	58.1	74.3
	SD	0.4	9.6	3.3	2.4	9.1	15.2	39.2	17.0
Fever + Breathing rate Temperature	Mean	92.0	61.1	81.2	85.5	42.1	87.9	74.8	77.5
	SD	0.9	7.9	3.0	1.7	5.1	15.4	30.2	16.9
Fever + Days with cough + Heart rate + Chest indrawing	Mean	91.6	68.3	83.4	82.7	62.1	94.0	74.0	84.4
	SD	0.3	6.6	2.7	3.4	7.7	12.1	23.3	8.8
Runny nose + Days with runny nose + BR + Temp	Mean	91.6	74.0	85.5	87.5	52.3	91.4	71.9	87.5
	SD	0.3	4.9	1.7	2.8	9.8	12.1	36.4	9.2
Runny nose + Days with runny nose + BR + Heart rate	Mean	91.6	61.8	81.2	84.0	47.6	85.9	59.4	74.6
	SD	0.3	3.2	1.6	2.8	3.3	21.2	37.6	17.7

The two best performing models for both age groups are compared in Figure 17.

For the single feature category, breathing rate and chest in-drawing (individually) still exhibit the best performance in general. The WHO/IMCI procedure implementation for this age group demonstrates S_n of 95.7±7.6% and S_p of 9.8±13.1%. The best double feature LRM models in this age group also include breathing rate as a parameter. The best two models are breathing rate with fever and breathing rate with oxygen saturation.

For triple features, the best testing performance was observed when using fever, temperature, and chest in-drawing. This combination reached a S_n of 92.1±15.8% and S_p of 51.3±39.0% for testing performance. The mean S_n is still comparable to the WHO criteria with 3% disparity, but the mean S_p of the LRM model is 423% higher.

The SD of the S_n is 107% larger compared to WHO, and for S_p it is 197% greater. The best S_p in this category is found in the combination of fever, breathing rate and temperature with S_p of 74.8%±30.2%. This is a 663% increase of mean S_p over WHO with 130% increase in SD. The mean S_n value is also 8% lower compared to WHO results while SD remains 100% higher.

In models with four features, the best performing model uses the existence of fever, number of days with cough, heart rate, and existence of chest in-drawing (S_n of 94.0±12.1% and S_p of 74.0±23.3%). The mean S_n is 2% lower than the WHO performance and the mean S_p is 655% higher. The second best performing model utilizes runny nose, days with runny nose, breathing rate, and temperature with S_n and S_p of 91.4±12.1% and 71.9±36.4%, respectively.

Recurrent features in best performing models

Following the recurrent appearance of certain features amongst the best performing LRMs in all feature combinations, we decided to systematically explore these features in order to rank the most significant features out of the 17 considered.

We set a threshold S_n of 90% and S_p of 70% on the mean testing performance for all possible combinations, from using one feature at a time to 17 features, and found 20 models that meet the criteria (eight models from the 2-11 month age group and 12 from the 12-60 age month group, respectively). Table 13 shows the number of recurrence for each feature within the top 20 feature combinations.

Table 13 – Number of feature occurrence in the models showing >90% S*n* and >70%S*p*.

No	Feature Name	[illegible] mths	60 mths
1	'Ageinmonths'	0	0
2	'Fever'	0	4
3	'Dayswithfever'	0	0
4	'Cough'	0	1
5	'Dayswithcough'	0	4
6	'Runnynose'	8	8
7	'Dayswithrunnynose'	8	8
8	'Breathingdifficulty'	0	1
9	'Dayswithbreathingdifficulty'	0	0
10	'Weight'	0	0
11	'Height'	0	0
12	'Breathingrate'	8	8
13	'Heartrate'	0	1
14	'Temperature'	8	8
15	'BMI'	4	5
16	'O2Saturation'	4	4
17	'Chestindrawing'	4	8

Several measurements such as the breathing rate and observations such as the existence of runny nose are dominantly present as recurrent features in good models.

DISCUSSION

One particular aim of this study was to explore if common clinical observations and measurements could be utilized to diagnose pneumonia at specificities higher than possible with the WHO procedure, while maintaining the sensitivity of at least 90%. Our results have illustrated that this is indeed possible. Our best performing models demonstrated a sensitivity of 91% while achieving an S_p in the range of 70-72% depending on the age of the subjects. These numbers represented 84-655% increase in S_p compared to the WHO/IMCI procedure, which had S_p ranging between 10-38%. Our results are based on k-fold cross validation, and the reported outcomes are thus not on the same data used to train a particular model.

The number of clinical observations and measurements needed to achieve a desired performance provides useful insight in designing clinical protocols targeting resource-poor areas. Results we obtained indicated that our single feature models perform similar to the WHO/IMCI procedure. Addition of second, third and fourth features significantly improve S_p while S_n continues to hold above 90%. Beyond four features, the calculation complexity rises without any performance gain.

One important contribution of this paper is the identification of most important clinical features and measurements that may substantially increase the accuracy of diagnosing pneumonia in resource-poor regions. We surveyed our exhaustive model database for the repeated appearance of features in models satisfying $S_n > 90\%$ and $S_p > 70\%$.

The breathing rate appeared as a feature in 16 models across both age groups. Oxygen saturation and chest in drawing too were important parameters appearing respectively in 8 and 12 models out of a total of 20. The significance of these measurements are well known among the medical and research communities. Our work uncovered two parameters of potential significance; "*the existence of runny nose*" and *the "number of days with runny nose"* both of which appeared in 16 out of 20 models, just like the breathing rate. The "*existence of fever*" also presented as a frequent parameter (4 out of 20 models) for the age group 12-60 months.

Breathing rate is the main measurement used in the WHO/IMCI procedure to diagnose pneumonia. While it appears an easy parameter to measure, it has been found difficult to achieve in resource-poor regions. Therefore, a major fraction of the global pneumonia diagnosis resources are allotted to improving technologies and protocols to measure the breathing rate[nn]. Without a reliable breathing rate measurement, the WHO/IMCI methods cannot be used in the field.

Our results suggest that while breathing rate is an important parameter, it is not essential to diagnose pneumonia. For instance, our model using the four features *age, existence of fever*, *existence of cough* and *days of cough* was capable of S_n = 83.5±14.5% and S_p = 67.3±23.9% respectively, for the 2-11 month age group. In the other age group, this model exhibited S_n and S_p of 91.7±17.8% and 51.0±34.6%, respectively. Among two-feature models, the combination using fever and days with cough resulted in S_n and S_p of 90.2±14.0% and 44.3±25.9%, respectively, for the 2-11 month age group. For the older age group, the model performed with S_n=85.5±15.2% and S_p=41.9±47.7%. These results corroborate our previous observation that breathing rate may not add additional value when mathematical features derived from cough sounds are available for diagnosing pneumonia[31].

Recently there has been a renewed interest in the use of pulse oximetry in reducing childhood pneumonia mortality in resource-poor settings [27-29]. Hypoxemia is a diagnostic indicator for severe pneumonia and swift access to oxygen treatment could improve the prognosis, when available. In our exhaustive model building process, we found 8 of the 20 best models included oximetry as a feature. Oximetry can be a highly useful feature. However, our results suggest that we can substitute, in its place, simpler feature combinations when a pulse oximeter is not available in the field. Examples features are the *existence of runny nose* and the *days of runny nose*.

The WHO/IMCI criteria for resource-poor regions have been designed to be highly sensitive to detect pneumonia (94% for those aged <24months, 62% for ≥24 months)[17]. A high number of false positive results also occur, reducing the specificity of the method (16-20%)[17]. In two of our previous works on children, we have seen WHO/IMCI performing at a sensitivity of 83% and a specificity of 47% (n=91) [25, 31]. The WHO/IMCI criteria works well when applied by doctors *in conjunction with* clinical and radiological analysis, giving performances of 77-81% sensitivity and 77-80% specificity [32]. These numbers are comparable with what we obtained in this paper, though our method did not use laboratory or radiological measurements.

Low specificity of the WHO criteria can lead to rising antimicrobial resistance in communities and render antibiotics ineffective. It also wastes rare drug stocks and delays early treatment opportunities for diseases with symptom overlap (e.g. malaria)[10, 33]. In low resource settings where only WHO/IMCI criteria are available, as many as 30% of cases had symptoms compatible with both malaria and pneumonia, necessitating dual treatment [34]. One of these treatments could be redundant. The method presented in this paper could potentially help with these issues by producing more accurate results, even in the absence of key parameters such as breathing rate.

The approach we took in this paper is unique. We systematically exhausted all possible feature combinations in our set of 17 features. Altogether we built and tested 131,071 models, each using different feature combinations. In the literature there are instances where WHO/IMCI procedure was augmented with one or two other handpicked clinical features (e.g. fever, oximetry) targeting manual interpretation. For instance, Cardoso et al in their 2010 study [17] added fever to WHO/IMCI procedure and illustrated the specificity increased up to 44% (age group <24 month) and 50% (age group 24-60 months). However, the sensitivity was reduced below that of WHO/IMCI. In particular, in the age group 24-60 months, neither the original WHO/IMCI nor the modified method could achieve sensitivity above 62%. The method we proposed can achieve a sensitivity above 90% while maintaining the specificity at the range 70-72%. No manual interpretation of features is necessary, and our method can provide a decision device.

In an independent development, Naydenova et al. published results on a method of combining several features using a machine learning approach[30]. They reported oxygen saturation, temperature, breathing rate and heart rate as leading to the best performance in their model (sensitivity 96.6%, specificity 96.4%). In our work, the same feature combination resulted in a much inferior performance (sensitivity 88.8%, specificity 40% in the age group 2-11 months; sensitivity 82.7% and specificity 35.4% in the age group 12-60 months).

One critical difference between our method and the one by Naydenova[30] is that they used healthy people as Control Subjects while we used children with respiratory symptoms satisfying inclusion criteria as our Control Subjects. Our Control Subjects were children who visited the hospital seeking treatment for illnesses with symptoms shared with pneumonia, but the medical diagnosis was they had different diseases. The research problem we explored was completely different from the one examined by Naydenova[30] and the results are thus not comparable. Separating normal children from pneumonia subjects is a much simpler problem compared to identifying pneumonia subjects from a group of children with a range of respiratory illnesses.

CONCLUSION

We have developed a method using logistic regression modelling to diagnose pneumonia based on various clinical features commonly recorded from patients. The LRM models we developed retain the high sensitivity of the WHO/IMCI procedure while increasing its mean specificity by 84% for the 2-11 month age group and 655% for the 12-60 month age group.

This study is currently limited by the number of subjects (n=134) involved in the study as well as the way pneumonia was diagnosed. The reference standard used in this study is the overall clinical diagnosis aided by auscultation, laboratory analysis and radiography (when deemed clinically necessary by the attending physician) and the clinical course of the subject's response to treatment. Due to the need limit radiation exposure to children, x-ray imaging was not performed on all subjects in the study.

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----------End of Appendix B ----------

In compliance with the statute, the invention has been described in language more or less specific to structural or methodical features. The term “comprises” and its variations, such as “comprising” and “comprised of” is used throughout in an inclusive sense and not to the exclusion of any additional features. It is to be understood that the invention is not limited to specific features shown or described since the means herein described herein comprises preferred forms of putting the invention into effect. The invention is, therefore, claimed in any of its forms or modifications within the proper scope of the appended claims appropriately interpreted by those skilled in the art.

Throughout the specification and claims (if present), unless the context requires otherwise, the term "substantially" or "about" will be understood to not be limited to the value for the range qualified by the terms.

Any embodiment of the invention is meant to be illustrative only and is not meant to be limiting to the invention. Therefore, it should be appreciated that various other changes and modifications can be made to any embodiment described without departing from the spirit and scope of the invention.

CLAIMS

1. A method for automatically providing a carer of a patient with a disease state diagnosis of the patient including the steps of:

providing a diagnostic application software product including a multiplicity of diagnostic models derived from investigation of a population containing disease state positive and non-disease state subjects;

operating an input/output interface of an electronic device including a memory storing the software product to prompt the carer for identification of a number of disease diagnostic parameters and values therefor for the patient;

operating a processor of the electronic device to select one of the diagnostic models from the memory based on the identified disease diagnostic parameters;

operating the processor to apply the values of the disease diagnostic parameters to the selected diagnostic model; and

presenting a diagnosis to the carer on the input/output interface based upon results of the application of the parameters to the selected diagnostic model for the carer to use in providing therapy to the patient.

2. A method according to claim 1, wherein said diagnostic parameters comprise: breathing rate, existence of fever, existence of runny nose, number of days with runny nose, number of days with cough, existence of chest indrawing, temperature, BMI (body mass index), and oxygen saturation level;

3. A method according to claim 1 or claim 2, including selecting one of the diagnostic models with reference to one or more look up tables correlating diagnostic performance of models against available diagnostic parameters.

4. A method according to any one of the preceding claims, including prompting for user choice of a diagnostic model optimized for “sensitivity”, “specificity” or “accuracy” wherein the method includes operating the electronic device to select one of the diagnostic models taking into account the optimization choice.

5. A method according to any one of the preceding claims, including operating the device to determine if the values of diagnostic parameters indicate patient danger signs.

6. A method according to claim 5, including checking if the diagnostic values for the patient indicate that the patient is presenting general danger signs according to World Health Guidelines.

7. A method according to any one of the preceding claims, including saving diagnostic results to a remote server whereby diagnostic results may be saved and compared from a plurality of diagnostic devices.

8. A method according to any one of the preceding claims, including prompting for recording of at least one patient cough sound.

9. A method according to any one of the preceding claims, including requiring the recording of no more than two patient cough sounds.

10. A method according to claim 8, including applying the at least one patient cough sound to a cough feature extraction engine of the diagnostic application to generate cough features.

11. A method according to claim 7 or 8, wherein patient cough features are applied to the diagnostic model to assist the diagnosis.

12. A method according to claim 1, wherein the diagnostic parameters comprise breathing rate, temperature, heart rate and cough sound analysis.

13. A diagnostic device arranged to prompt a clinician to input diagnostic information for a patient and further arranged to automatically present a diagnosis to the clinician, the diagnostic device including:

an electronic memory storing instructions comprising a diagnostic application software product including a plurality of diagnostic models derived from investigation of pneumonia-positive and non-pneumonia subjects;

an electronic processor in communication with the electronic memory for executing the instructions;

a user interface responsive to the electronic processor for the processor to prompt for and receive the diagnostic information;

wherein the processor is configured by the diagnostic application in use to present a diagnosis of the patient with the user interface by applying the diagnostic information to at least one of said diagnostic models.

14. A method according to claim 13, wherein the diagnostic device includes a microphone and audio interface coupling the microphone to the electronic processor.

15. A method according to claim 13, wherein the diagnostic application includes a cough feature extraction engine and whereby in use the processor applies the cough sound to the cough feature extraction engine to produce cough features thereof.

16. A method according to claim 14, wherein the diagnostic device is configured by the diagnostic application in use to apply the cough features to the at least one of said diagnostic models.

17. A method of automatically diagnosing pneumonia in a patient comprising:

using an input/output interface device to obtain values of two or more diagnostic parameters of the patient from a carer for the patient;

said diagnostic parameters comprising: breathing rate, existence of fever, existence of runny nose, number of days with runny nose, number of days with cough, existence of chest indrawing, temperature, BMI (body mass index), and oxygen saturation level;

using a processor device operatively coupled to the input/output interface to apply the two or more diagnostic parameters to an electronic memory storing a plurality of precompiled pneumonia diagnostic models to thereby identify an optimal diagnostic model of said plurality;

applying the values of the two or more diagnostic signs to the identified optimal diagnostic model to generate a diagnosis output from the diagnostic model; and

operating the input/output interface device in accordance with the diagnosis output to indicate presence or absence of pneumonia in the patient to the carer, for use by the carer in providing care to the patient;

wherein the pneumonia diagnostic models are derived from investigation of a population of pneumonia positive patients and non-pneumonia positive subjects.

* * *

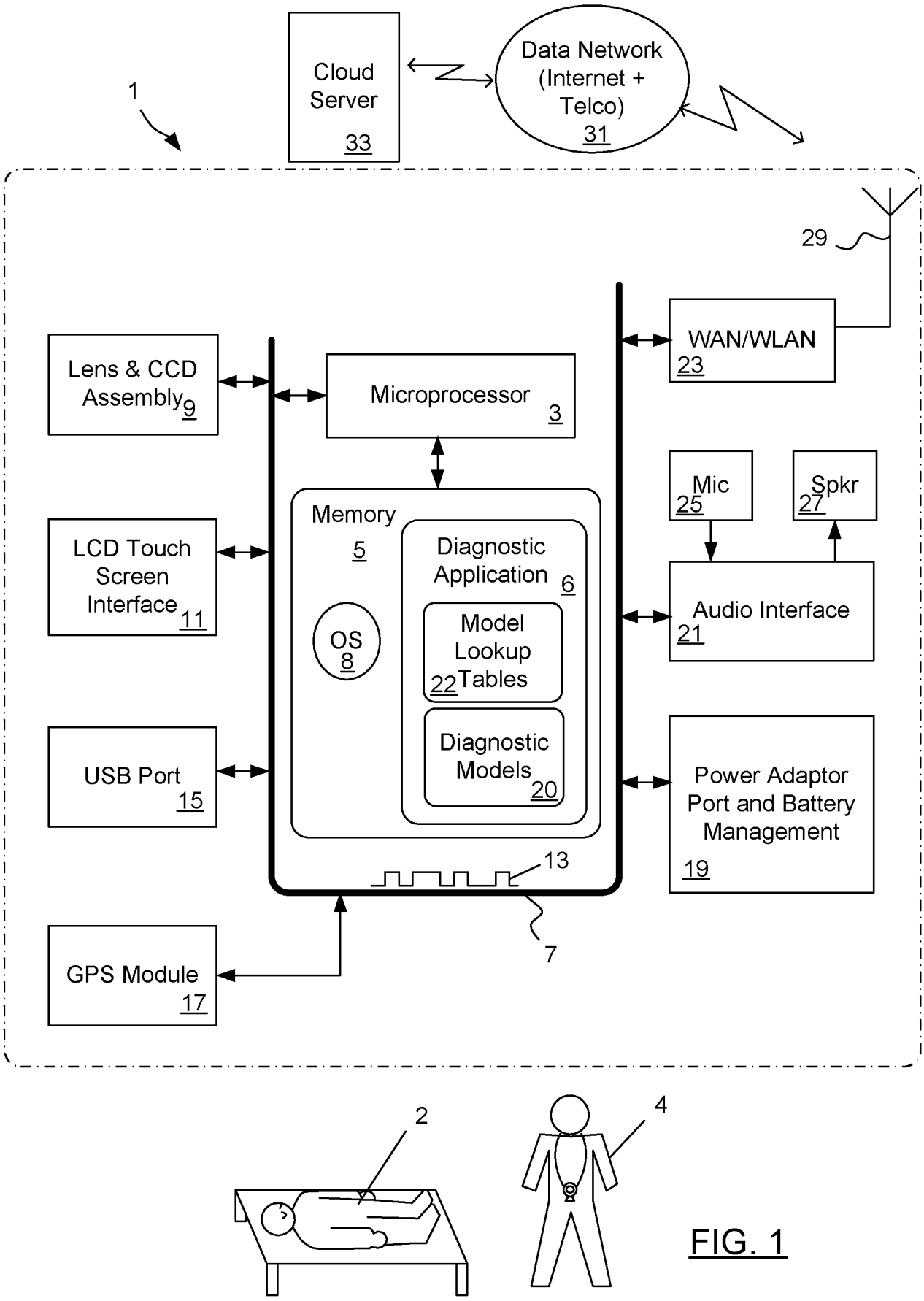

1
Cloud Server 33
Data Network (Internet + Telco) 31
29
WAN/WLAN 23
Lens & CCD Assembly 9
Microprocessor 3
Mic 25
Spkr 27
Memory 5
Diagnostic Application 6
LCD Touch Screen Interface 11
OS 8
Model Lookup Tables 22
Audio Interface 21
USB Port 15
Diagnostic Models 20
Power Adaptor Port and Battery Management 19
13
7
GPS Module 17
2
4

FIG. 1

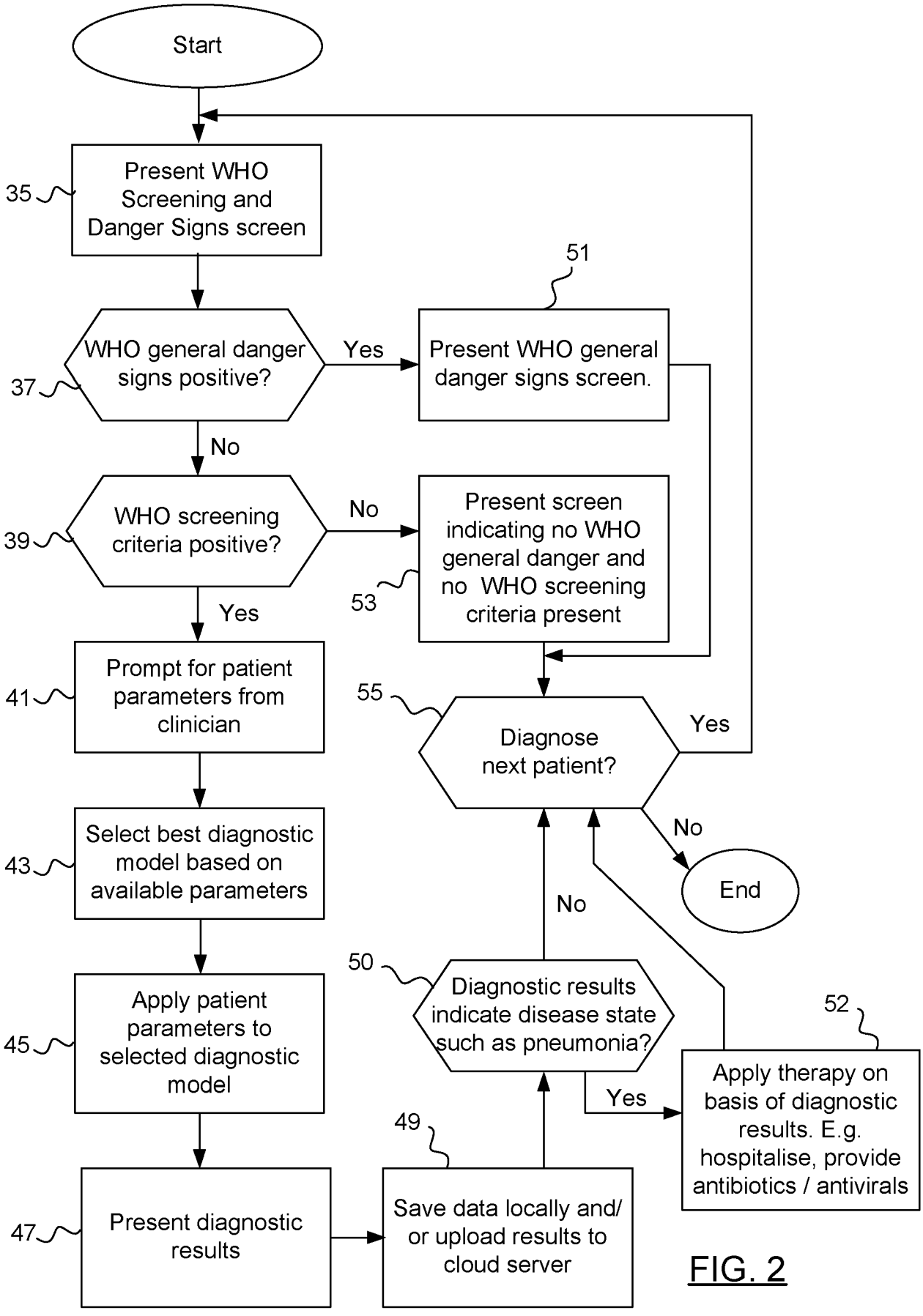

Start
Present WHO Screening and Danger Signs screen
35
WHO general danger signs positive?
37
Yes
Present WHO general danger signs screen.
51
No
WHO screening criteria positive?
39
No
Present screen indicating no WHO general danger and no WHO screening criteria present
53
Yes
Prompt for patient parameters from clinician
41
Diagnose next patient?
55
Yes
No
End
Select best diagnostic model based on available parameters
43
Apply patient parameters to selected diagnostic model
45
Diagnostic results indicate disease state such as pneumonia?
50
No
Yes
Apply therapy on basis of diagnostic results. E.g. hospitalise, provide antibiotics / antivirals
52
Present diagnostic results
47
Save data locally and/ or upload results to cloud server
49

FIG. 2

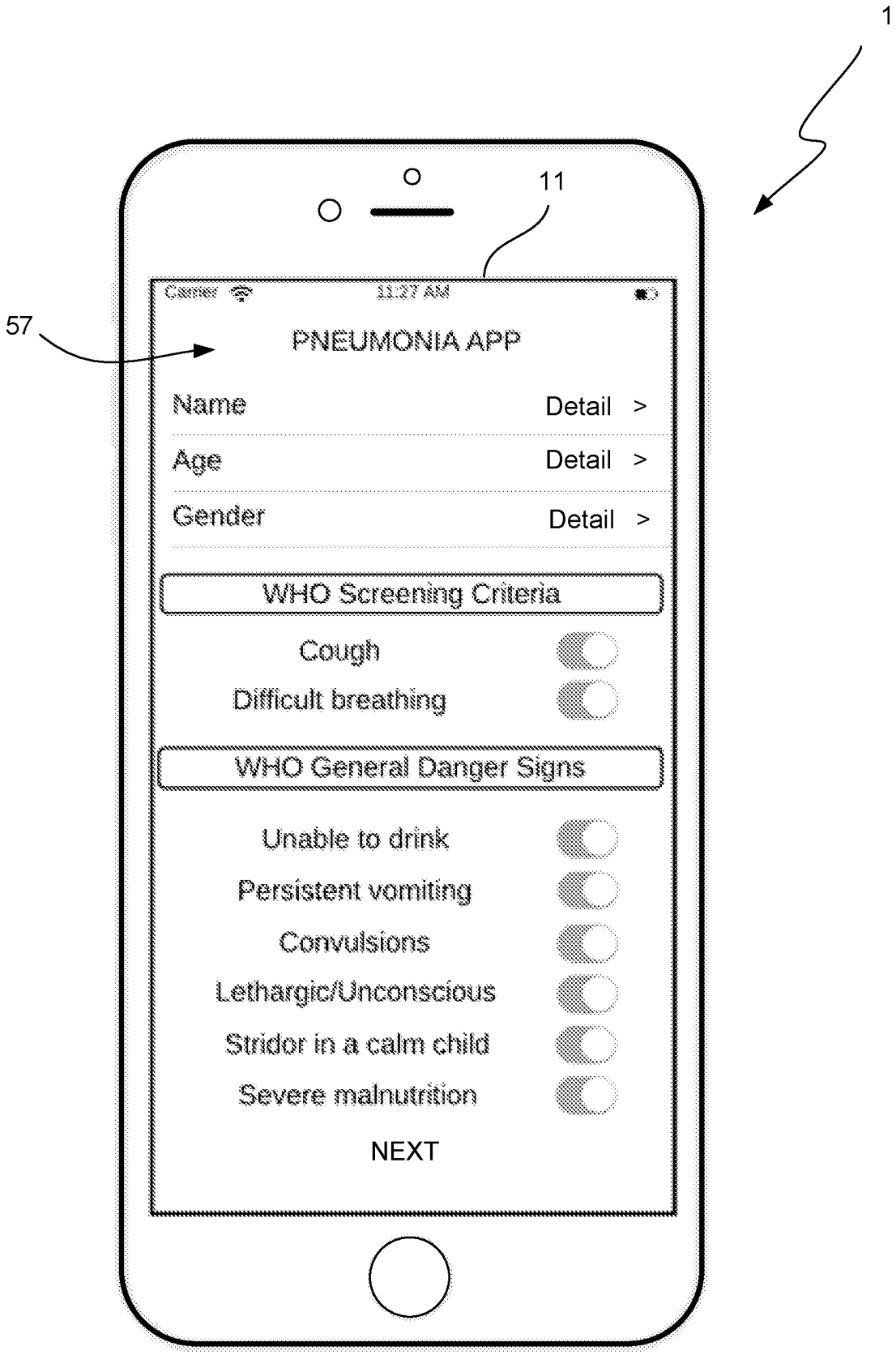

1
11
57
Carrier
11:37 AM
PNEUMONIA APP
Name
Detail >
Age
Detail >
Gender
Detail >
WHO Screening Criteria
Cough
Difficult breathing
WHO General Danger Signs
Unable to drink
Persistent vomiting
Convulsions
Lethargic/Unconscious
Stridor in a calm child
Severe malnutrition
NEXT

FIG. 3

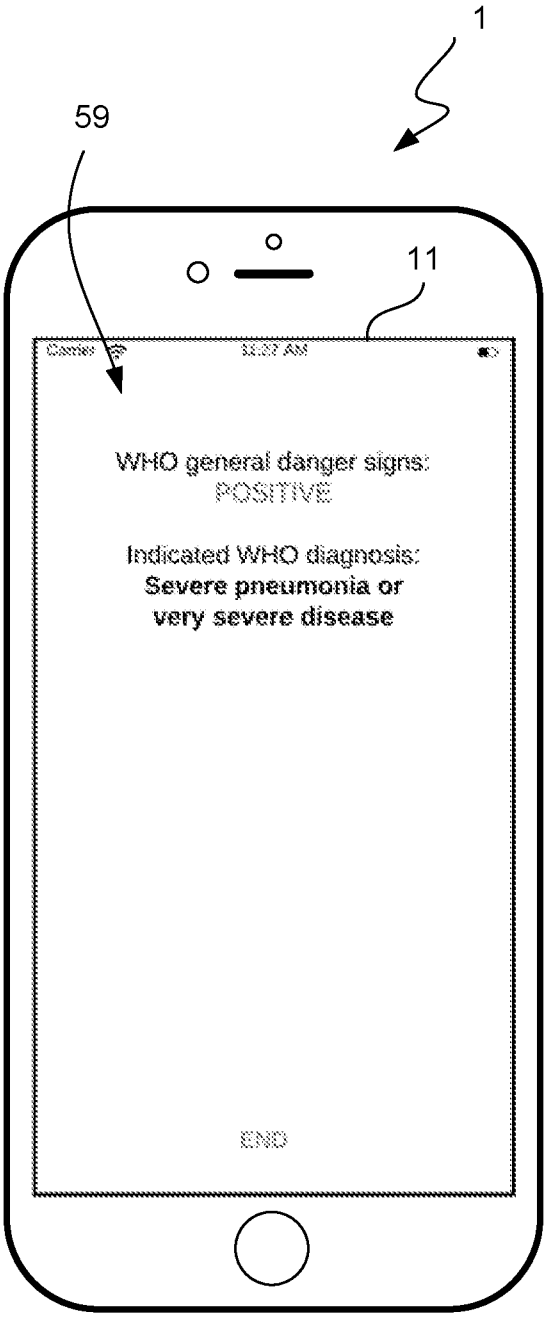

1
59
11
WHO general danger signs:
POSITIVE
Indicated WHO diagnosis:
Severe pneumonia or
very severe disease
END

FIG. 4

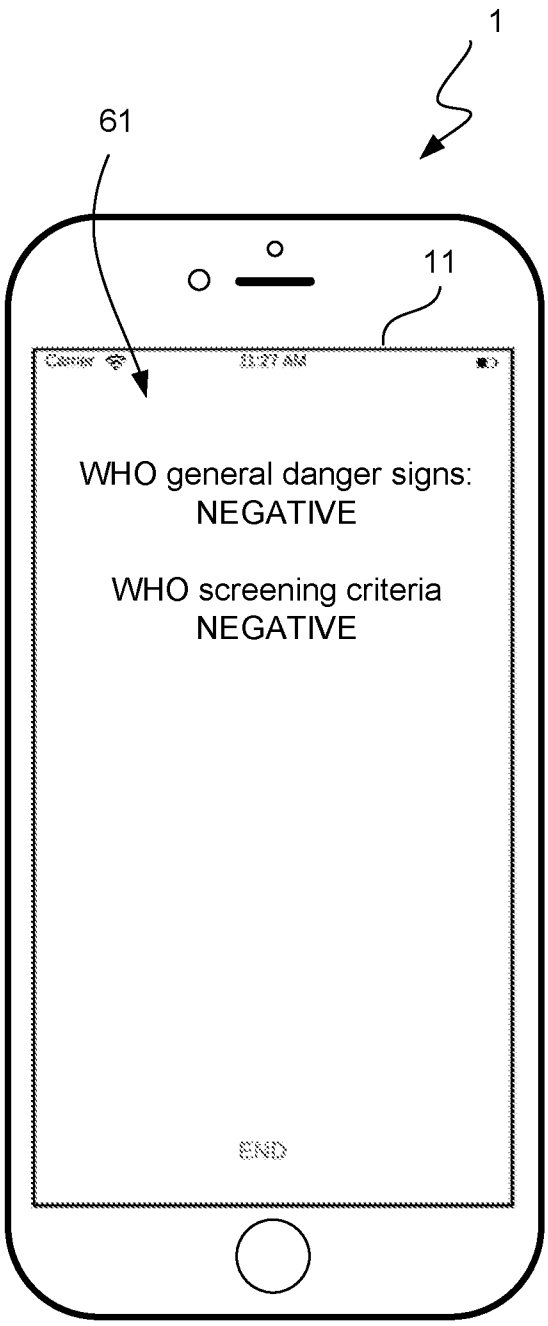

1
61
11
WHO general danger signs:
NEGATIVE
WHO screening criteria
NEGATIVE
END

FIG. 5

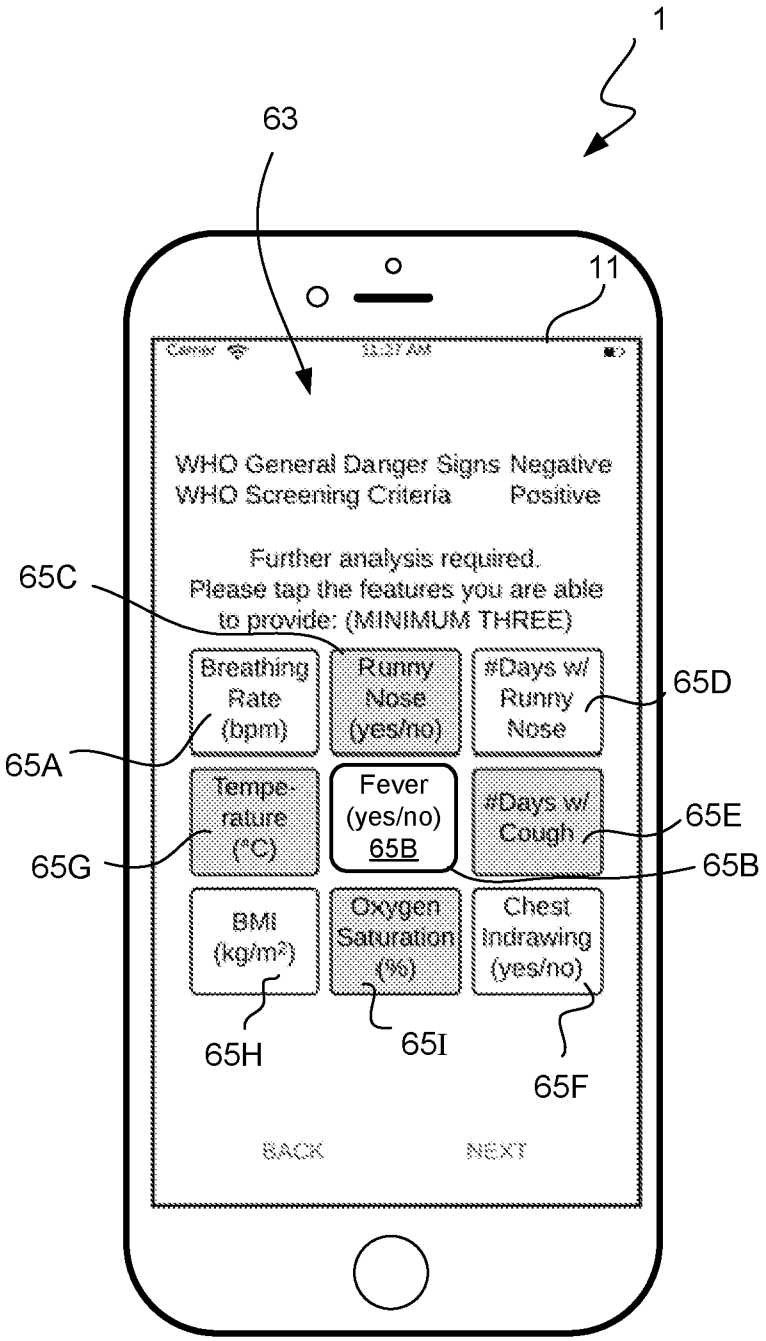

1
63
11
WHO General Danger Signs Negative
WHO Screening Criteria Positive
Further analysis required.
Please tap the features you are able to provide: (MINIMUM THREE)
Breathing Rate (bpm)
Runny Nose (yes/no)
#Days w/ Runny Nose
Tempe-rature (°C)
Fever (yes/no) 65B
#Days w/ Cough
BMI (kg/m²)
Oxygen Saturation (%)
Chest Indrawing (yes/no)
65A
65C
65D
65E
65G
65B
65H
65I
65F
BACK
NEXT

FIG. 6

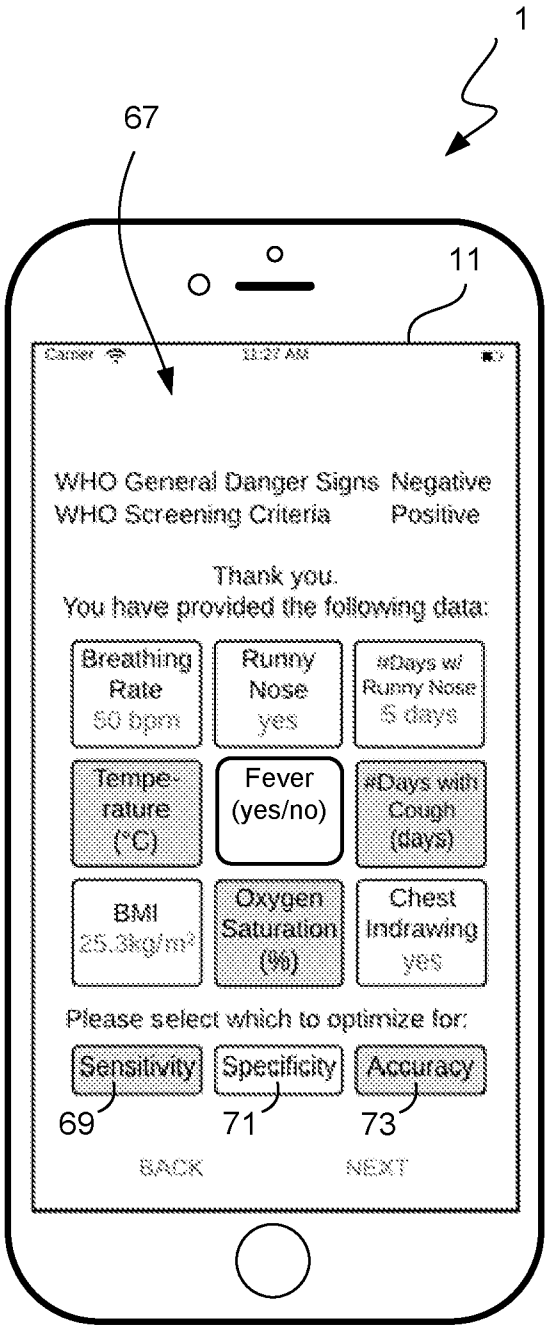

1
67
11
WHO General Danger Signs Negative
WHO Screening Criteria Positive
Thank you.
You have provided the following data:
Breathing Rate 50 bpm
Runny Nose yes
#Days w/ Runny Nose 5 days
Tempe-rature (°C)
Fever (yes/no)
#Days with Cough (days)
BMI 25.3kg/m²
Oxygen Saturation (%)
Chest Indrawing yes
Please select which to optimize for:
Sensitivity
Specificity
Accuracy
69
71
73
BACK
NEXT

FIG. 7

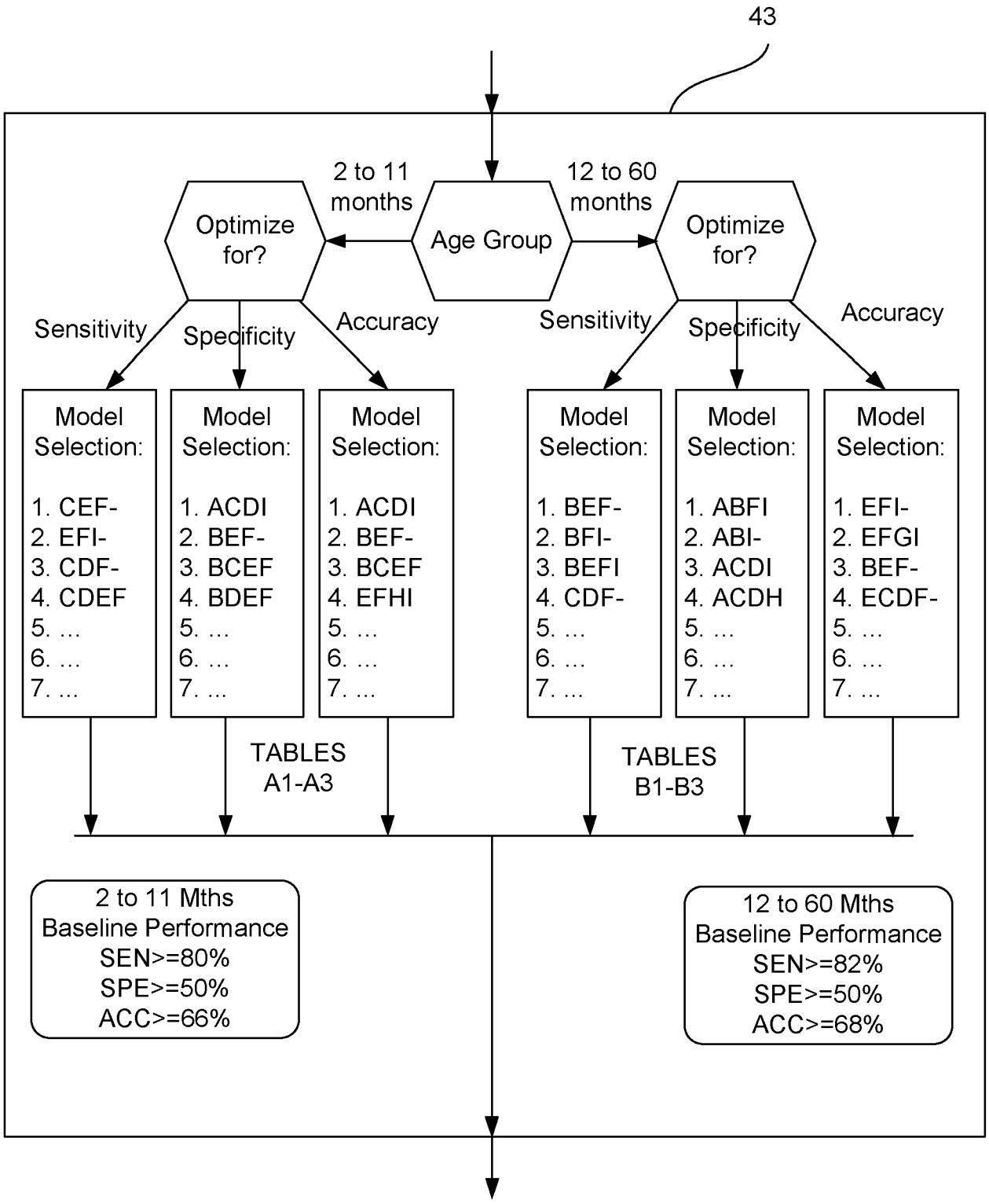

43
Age Group
2 to 11 months
12 to 60 months
Optimize for?
Optimize for?
Sensitivity
Specificity
Accuracy
Sensitivity
Specificity
Accuracy
Model Selection:
1. CEF-
2. EFI-
3. CDF-
4. CDEF
5. ...
6. ...
7. ...
Model Selection:
1. ACDI
2. BEF-
3. BCEF
4. BDEF
5. ...
6. ...
7. ...
Model Selection:
1. ACDI
2. BEF-
3. BCEF
4. EFHI
5. ...
6. ...
7. ...
Model Selection:
1. BEF-
2. BFI-
3. BEFI
4. CDF-
5. ...
6. ...
7. ...
Model Selection:
1. ABFI
2. ABI-
3. ACDI
4. ACDH
5. ...
6. ...
7. ...
Model Selection:
1. EFI-
2. EFGI
3. BEF-
4. ECDF-
5. ...
6. ...
7. ...
TABLES A1-A3
TABLES B1-B3
2 to 11 Mths Baseline Performance SEN>=80% SPE>=50% ACC>=66%
12 to 60 Mths Baseline Performance SEN>=82% SPE>=50% ACC>=68%

FIG. 8

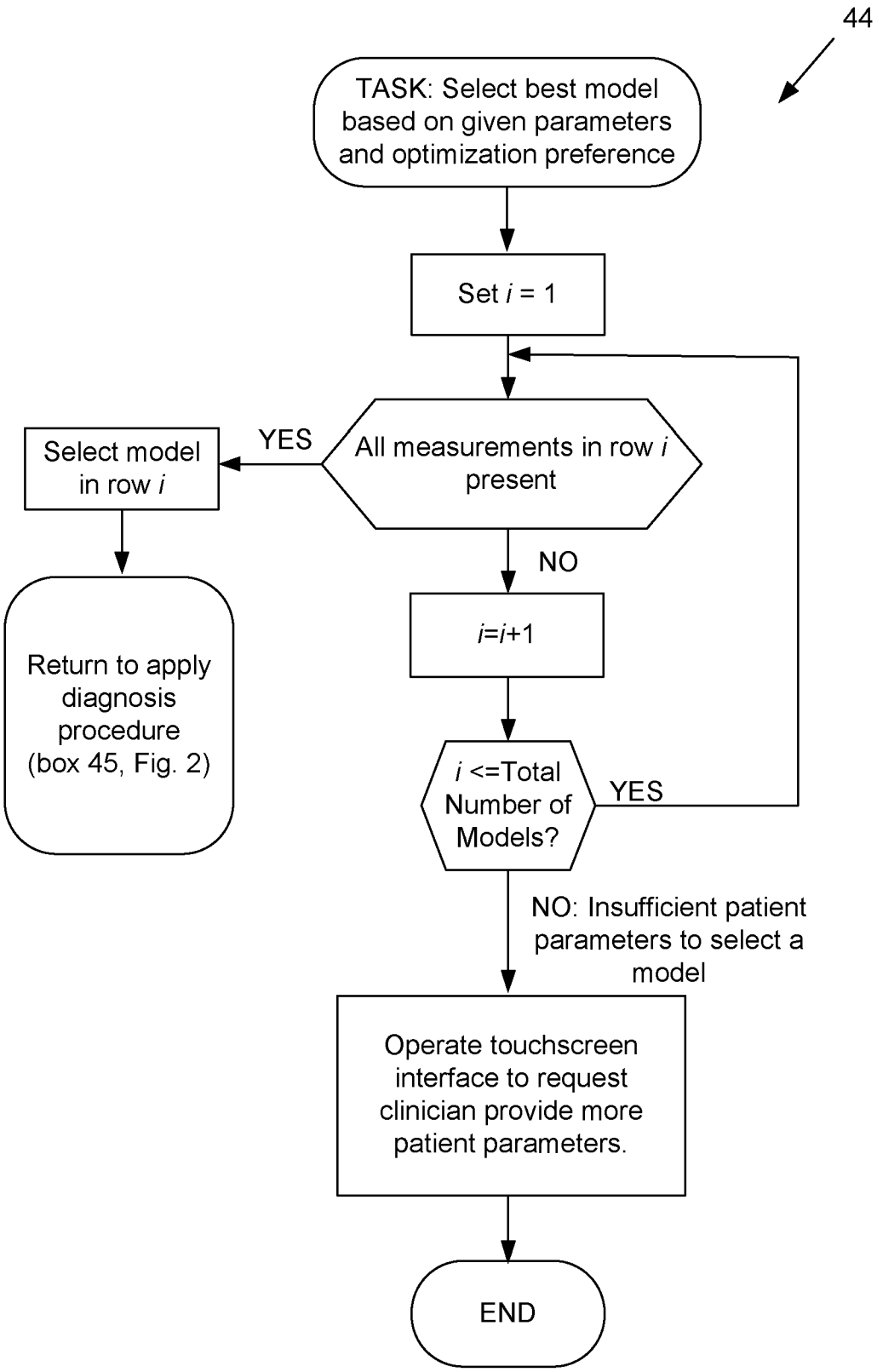

44
TASK: Select best model based on given parameters and optimization preference
Set i = 1
All measurements in row i present
YES
Select model in row i
Return to apply diagnosis procedure (box 45, Fig. 2)
NO
i=i+1
i <=Total Number of Models?
YES
NO: Insufficient patient parameters to select a model
Operate touchscreen interface to request clinician provide more patient parameters.
END

FIG. 9

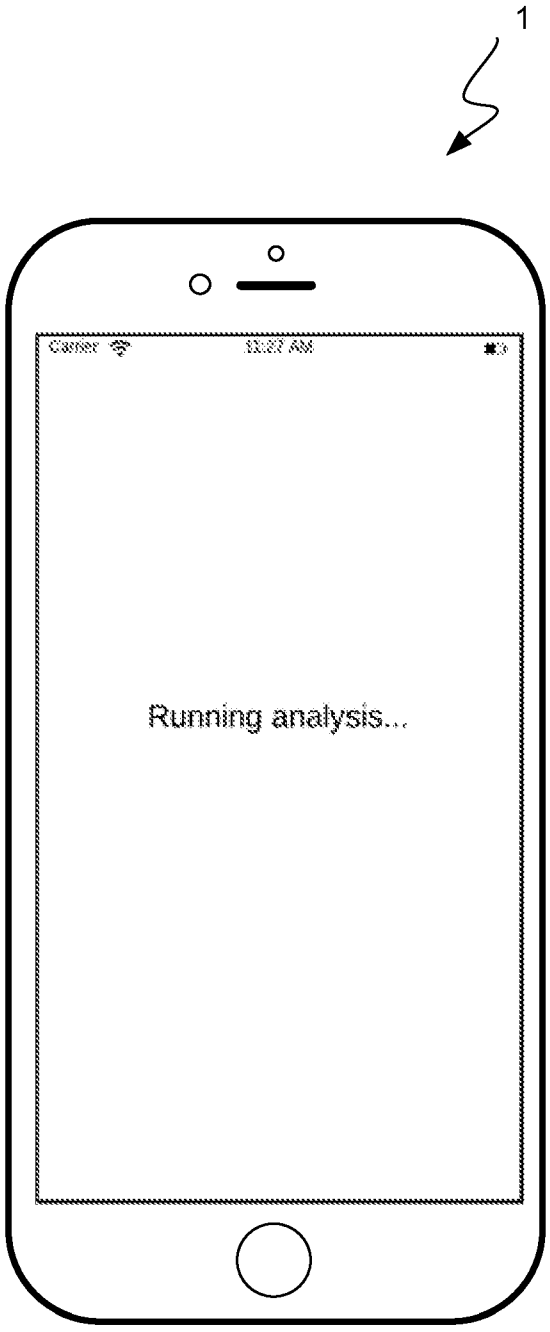

1
Carrier
10:27 AM
Running analysis...

FIG. 10

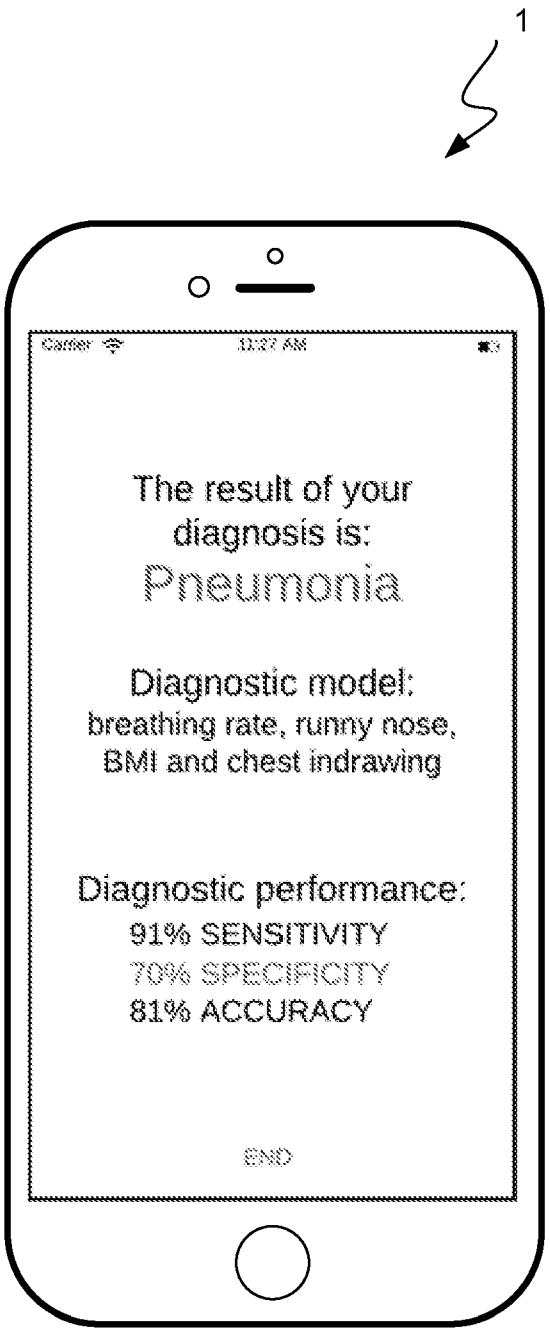
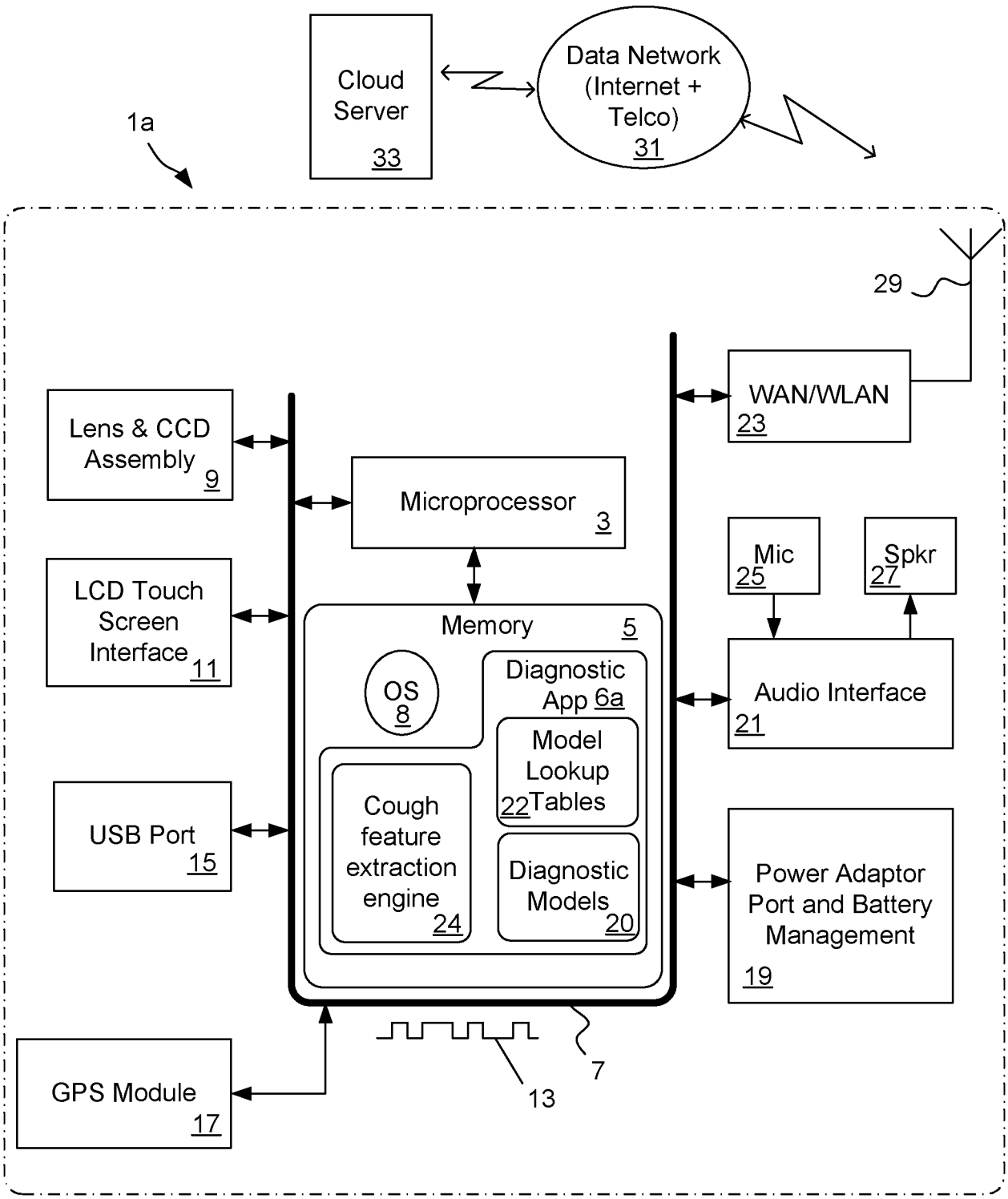

1
Carrier
10:27 AM
The result of your diagnosis is:
Pneumonia
Diagnostic model:
breathing rate, runny nose, BMI and chest indrawing
Diagnostic performance:
91% SENSITIVITY
70% SPECIFICITY
81% ACCURACY
END

FIG. 11


Cloud Server 33
Data Network (Internet + Telco) 31
1a
29
WAN/WLAN 23
Lens & CCD Assembly 9
Microprocessor 3
Mic 25
Spkr 27
LCD Touch Screen Interface 11
Memory 5
OS 8
Diagnostic App 6a
Model Lookup Tables 22
Audio Interface 21
Cough feature extraction engine 24
Diagnostic Models 20
USB Port 15
Power Adaptor Port and Battery Management 19
GPS Module 17
7
13

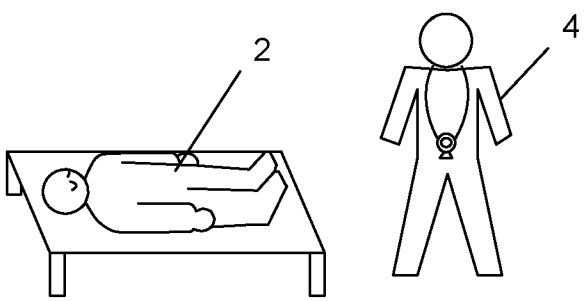

2
4

FIG. 11A

FIG. 11B

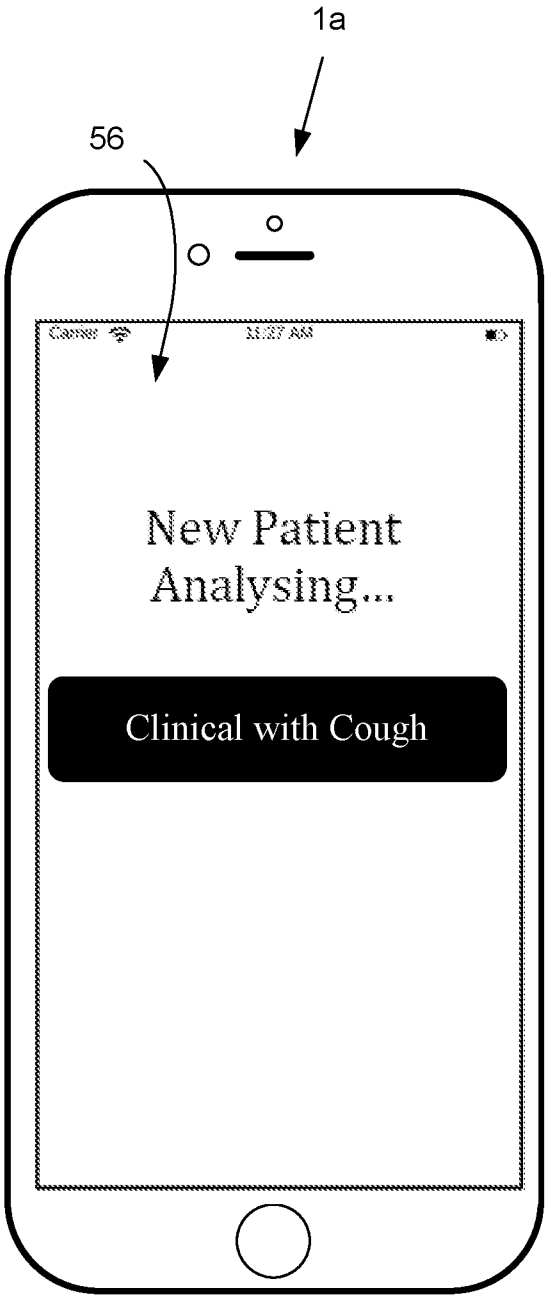


FIG. 11C

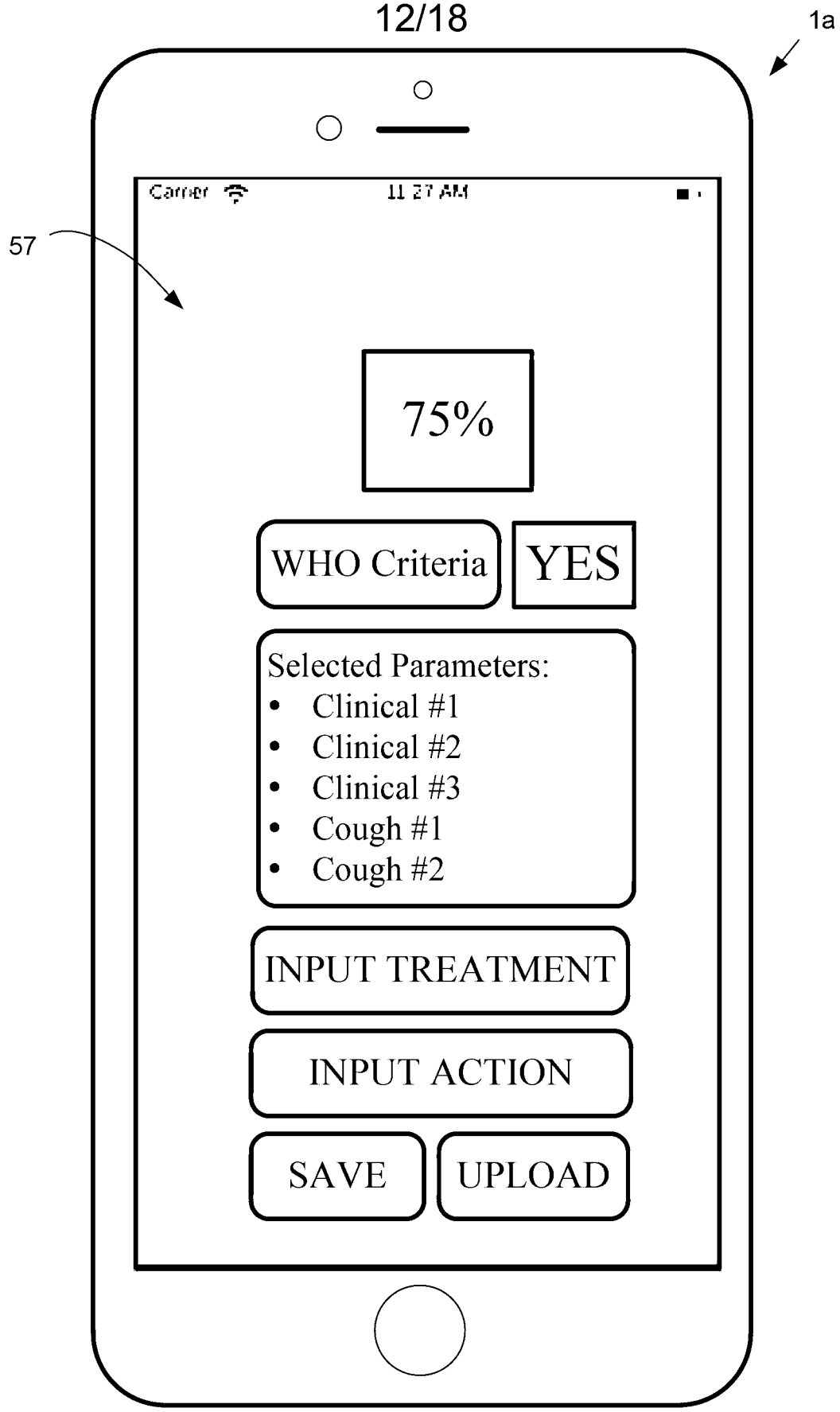

1a
57
Carrier
11:27 AM
75%
WHO Criteria
YES
Selected Parameters:
• Clinical #1
• Clinical #2
• Clinical #3
• Cough #1
• Cough #2
INPUT TREATMENT
INPUT ACTION
SAVE
UPLOAD

FIG. 11D

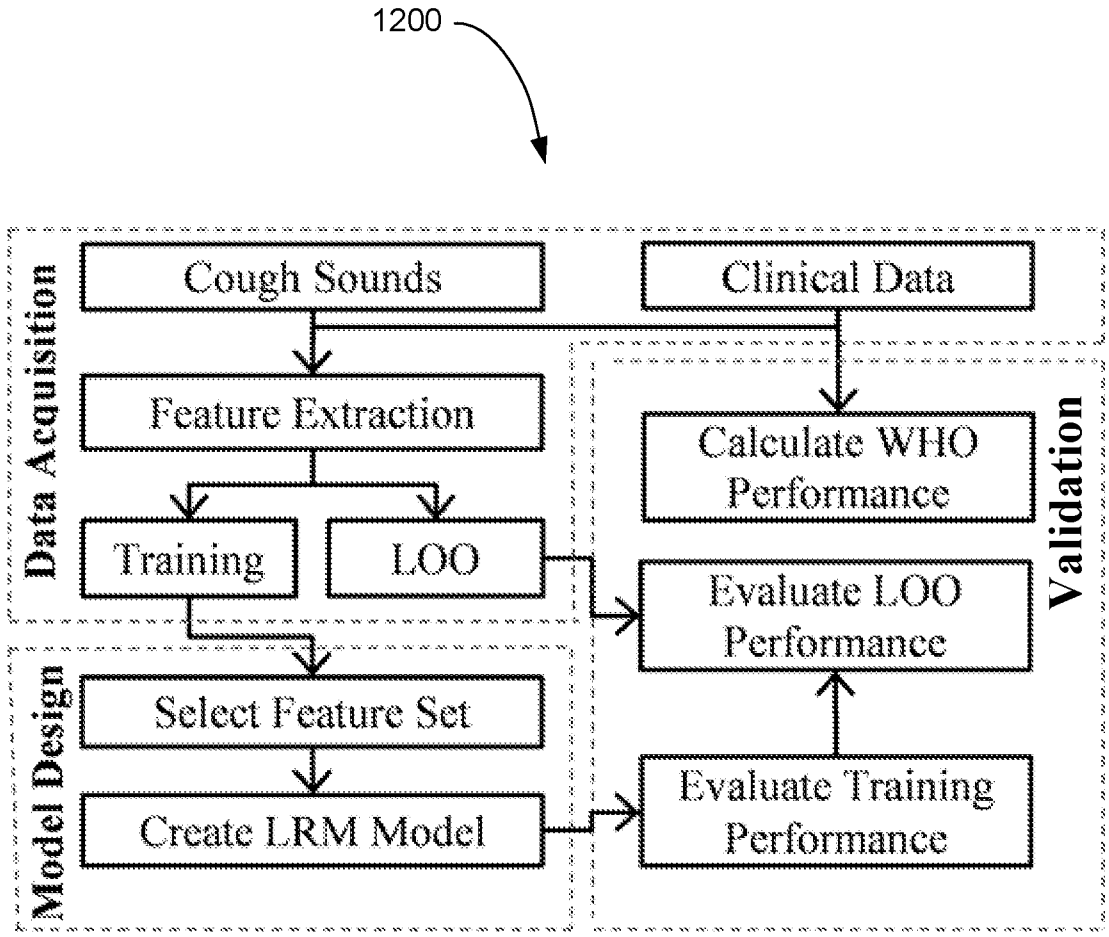

1200
Data Acquisition
Cough Sounds
Clinical Data
Feature Extraction
Training
LOO
Model Design
Select Feature Set
Create LRM Model
Validation
Calculate WHO Performance
Evaluate LOO Performance
Evaluate Training Performance

FIG. 12

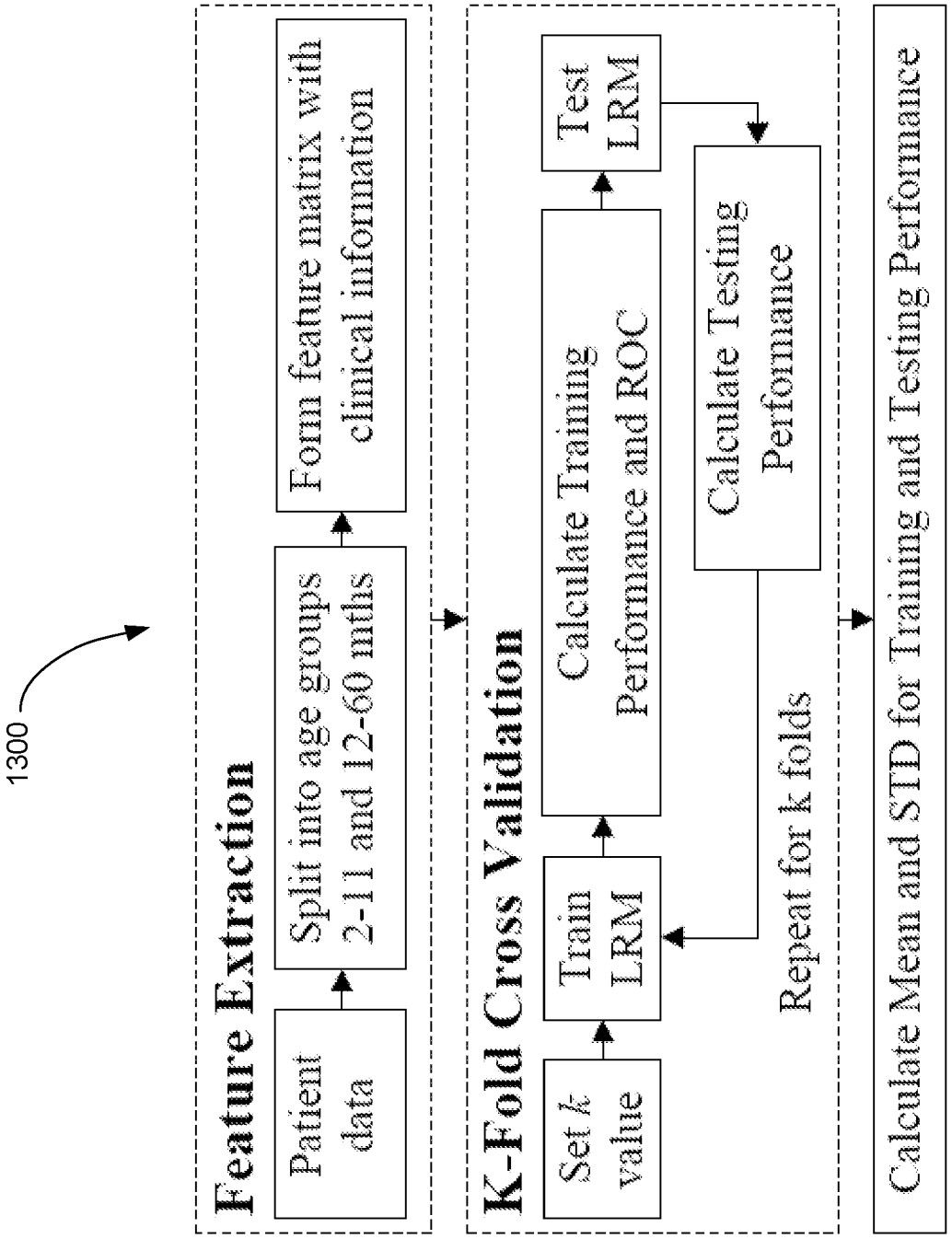

1300
Feature Extraction
Patient data
Split into age groups 2-11 and 12-60 mths
Form feature matrix with clinical information
K-Fold Cross Validation
Set k value
Train LRM
Calculate Training Performance and ROC
Test LRM
Calculate Testing Performance
Repeat for k folds
Calculate Mean and STD for Training and Testing Performance

FIG. 13

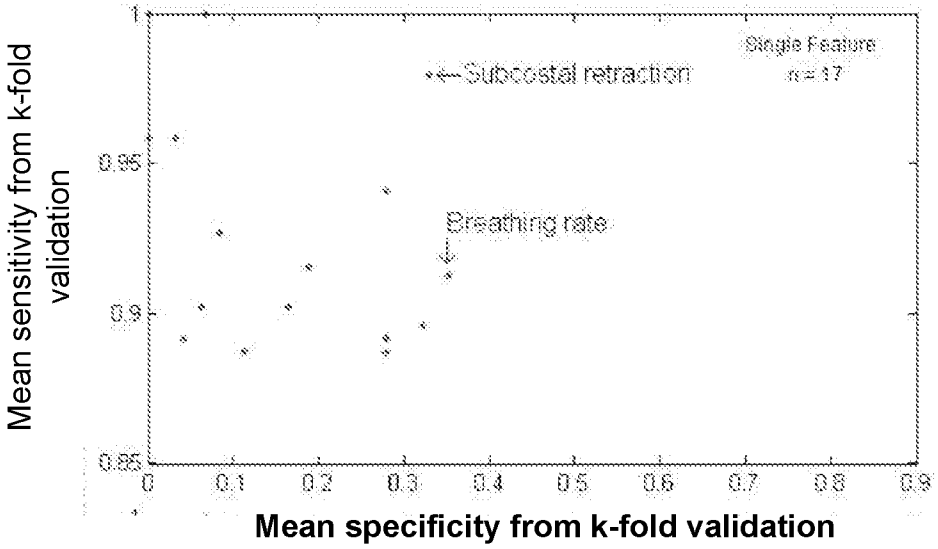


FIG. 14A

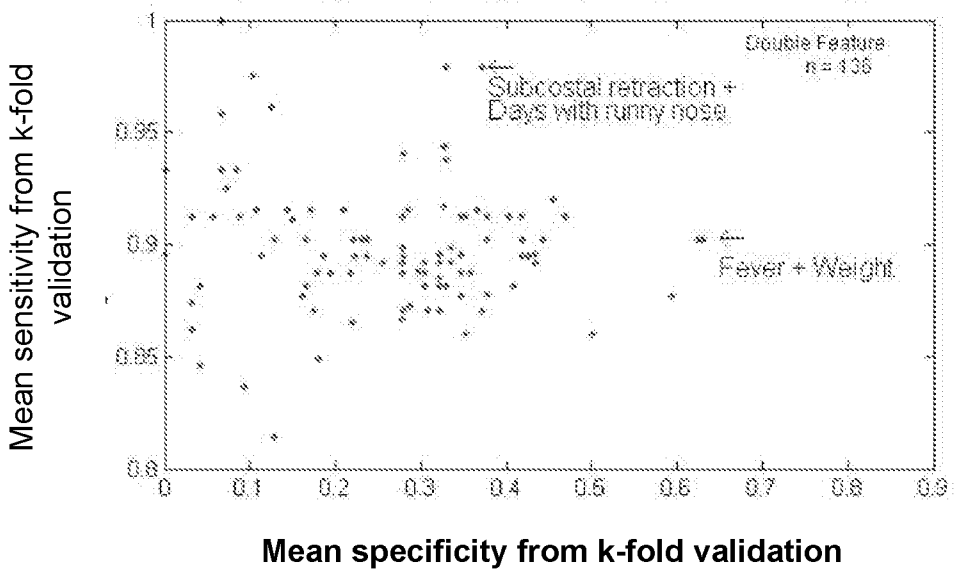


FIG. 14B

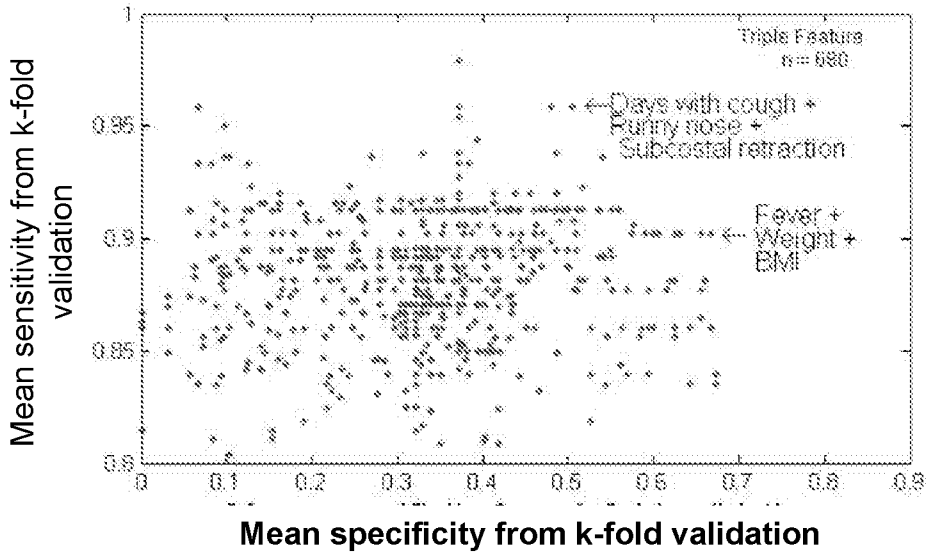


FIG. 14C

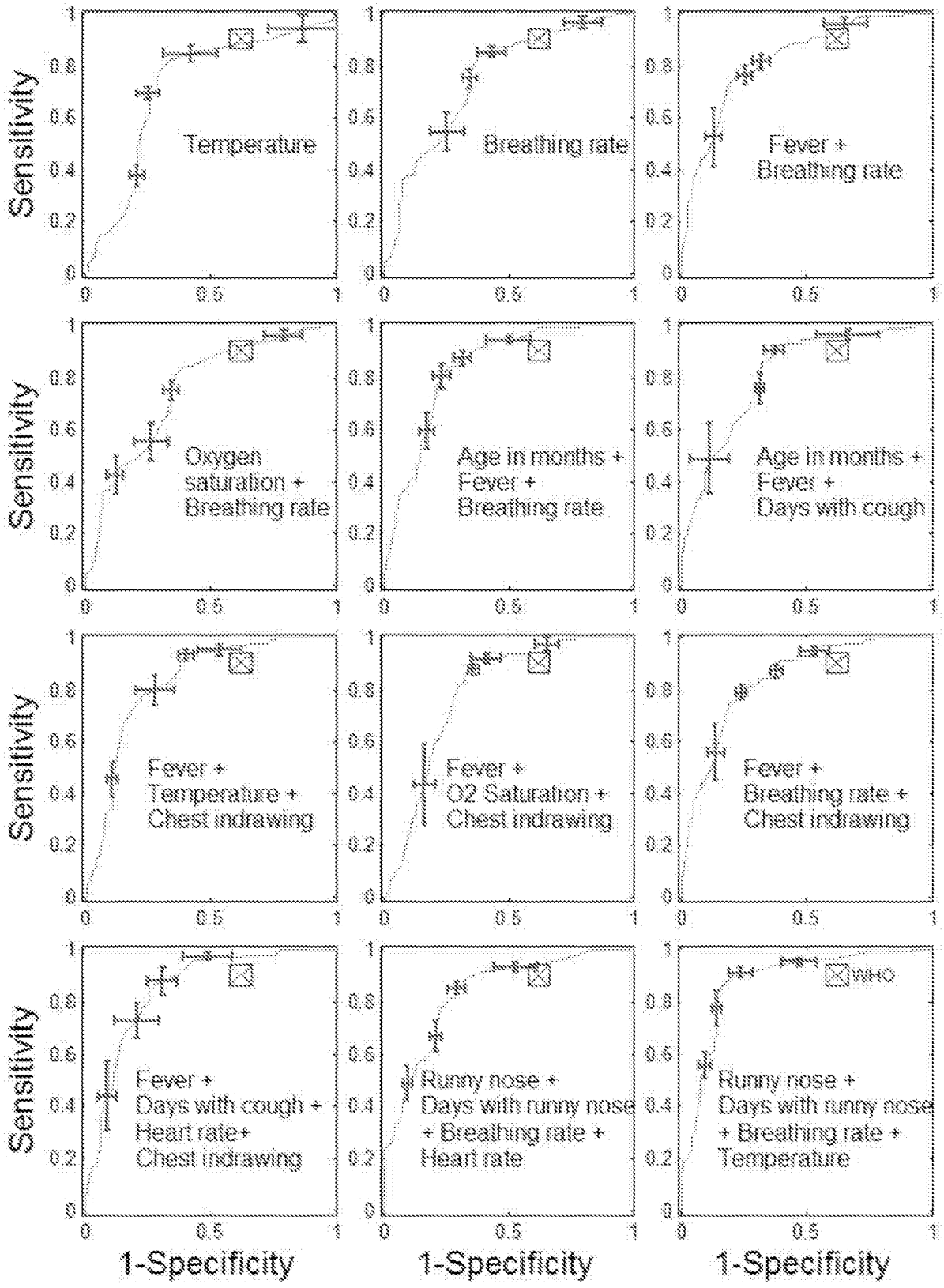

Sensitivity
Temperature
Breathing rate
Fever + Breathing rate
Oxygen saturation + Breathing rate
Age in months + Fever + Breathing rate
Age in months + Fever + Days with cough
Fever + Temperature + Chest indrawing
Fever + O2 Saturation + Chest indrawing
Fever + Breathing rate + Chest indrawing
Fever + Days with cough + Heart rate+ Chest indrawing
Runny nose + Days with runny nose + Breathing rate + Heart rate
WHO
Runny nose + Days with runny nose + Breathing rate + Temperature
1-Specificity
1-Specificity
1-Specificity

FIG. 15

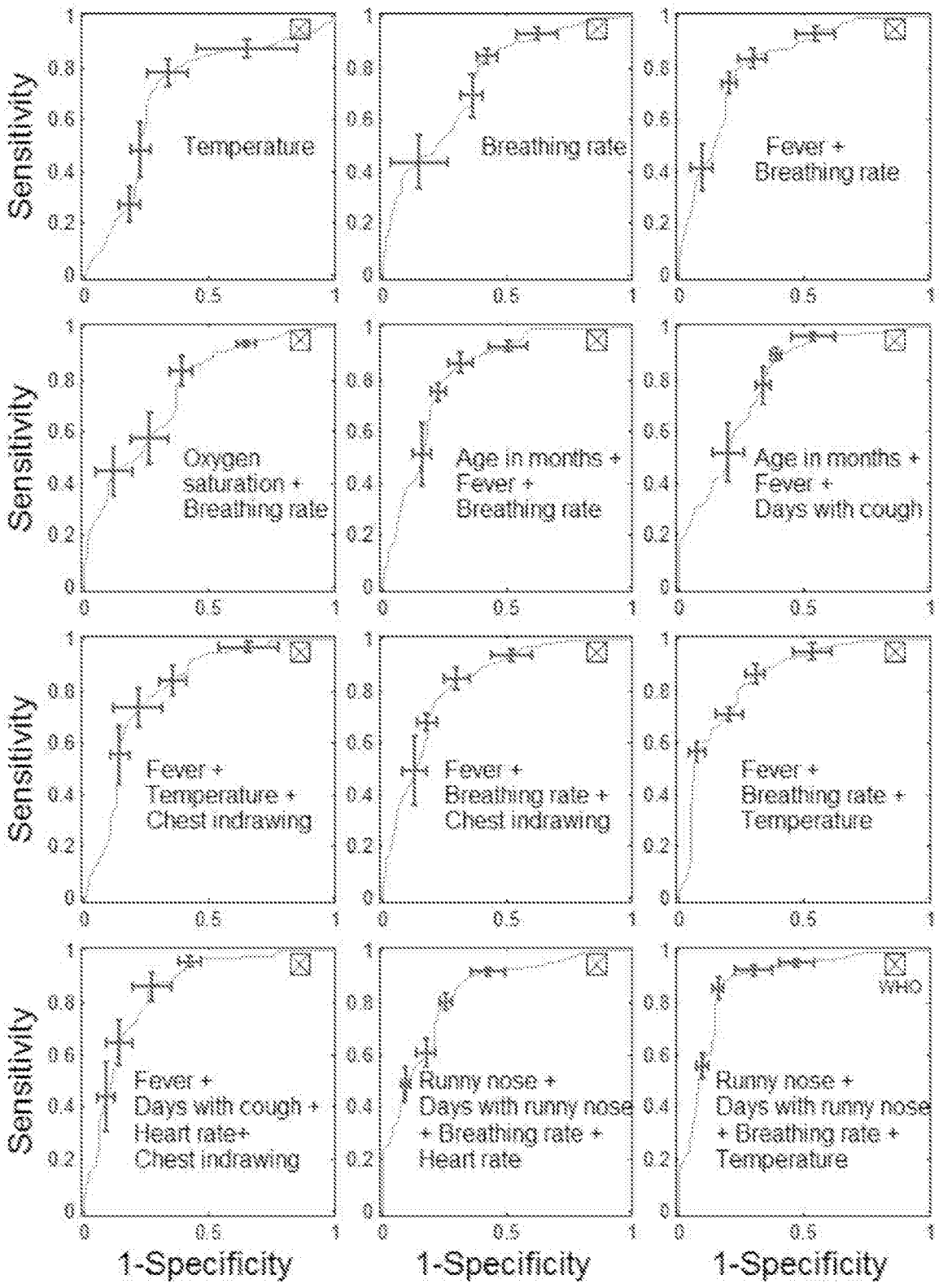

Sensitivity
Temperature
Breathing rate
Fever +
Breathing rate
Oxygen
saturation +
Breathing rate
Age in months +
Fever +
Breathing rate
Age in months +
Fever +
Days with cough
Fever +
Temperature +
Chest indrawing
Fever +
Breathing rate +
Chest indrawing
Fever +
Breathing rate +
Temperature
Fever +
Days with cough +
Heart rate+
Chest indrawing
Runny nose +
Days with runny nose
+ Breathing rate +
Heart rate
WHO
Runny nose +
Days with runny nose
+ Breathing rate +
Temperature
1-Specificity
1-Specificity
1-Specificity

FIG. 16

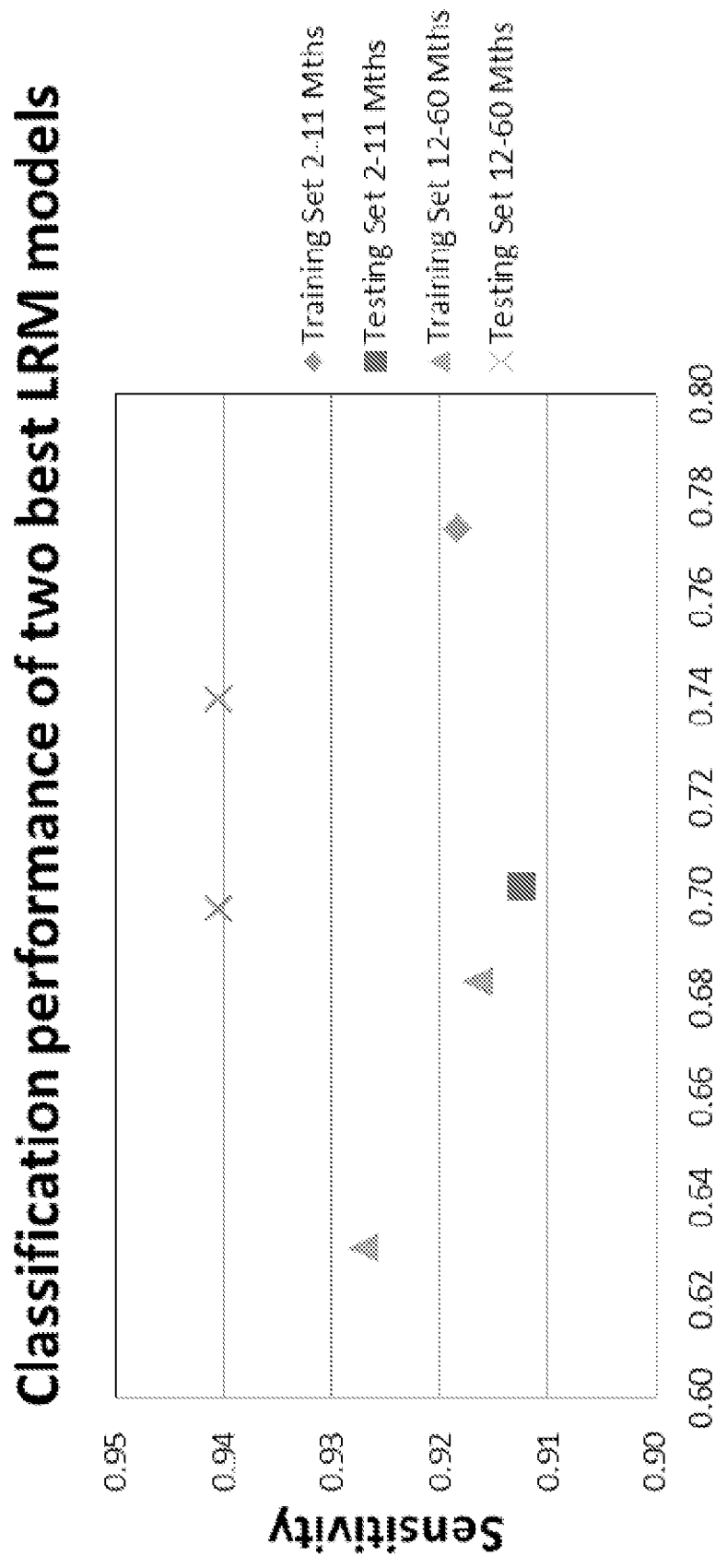

Classification performance of two best LRM models
Training Set 2-11 Mths
Testing Set 2-11 Mths
Training Set 12-60 Mths
Testing Set 12-60 Mths
Sensitivity
0.95
0.94
0.93
0.92
0.91
0.90
Specificity
0.60
0.62
0.64
0.66
0.68
0.70
0.72
0.74
0.76
0.78
0.80

FIG. 17

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2017/051048

A. CLASSIFICATION OF SUBJECT MATTER

A61B 5/00(2006.01)i, A61B 5/01(2006.01)i, A61B 5/1455(2006.01)i, A61B 5/024(2006.01)i, H04M 1/725(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61B 5/00; A61B 5/01; G06Q 50/00; A61B 5/1455; A61B 5/024; H04M 1/725

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) & Keywords: diagnostic, automatic, disease, parameter, input

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2014-0257058 A1 (SCANADU INCORPORATED) 11 September 2014 See paragraphs [36]-[67], [134]-[155]; claim 1 and figures 1-9.	13-17
Y		1-3,12
Y	JP 2007-018460 A (INFOCOM CORP.) 25 January 2007 See paragraphs [11]-[40] and figure 1.	1-3,12
A	JP 2009-110282 A (TOSHIBA CORP. et al.) 21 May 2009 See paragraphs [11]-[45] and figures 1-6.	1-3,12-17
A	US 2011-0270050 A1 (MORTEZA NAGHAVI et al.) 03 November 2011 See paragraphs [22]-[28] and figures 1-3.	1-3,12-17
A	US 2012-0215076 A1 (YANG CHANG-MING et al.) 23 August 2012 See claims 1-6 and figures 1-4.	1-3,12-17

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
02 February 2018 (02.02.2018)	**05 February 2018 (05.02.2018)**

Name and mailing address of the ISA/KR
International Application Division
Korean Intellectual Property Office
189 Cheongsa-ro, Seo-gu, Daejeon, 35208, Republic of Korea
Facsimile No. +82-42-481-8578

Authorized officer
Kim, Yeonkyung
Telephone No. +82-42-481-3325

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2017/051048

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 6,10
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
claims 6 and 10 do not comply with PCT Article 6 because they are referring to claims 5 and 8, respectively, which does not comply with PCT Rule 6.4(a).

3. ☒ Claims Nos.: 4,5,7-9,11
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required addtional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of any additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/AU2017/051048

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2014-0257058 A1	11/09/2014	WO 2013-066642 A1	10/05/2013
JP 2007-018460 A	25/01/2007	JP 4866576 B2	01/02/2012
JP 2009-110282 A	21/05/2009	JP 5159250 B2	06/03/2013
US 2011-0270050 A1	03/11/2011	None	
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		WO 2011-020216 A1	24/02/2011
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摘要(译)

一种自动诊断患者的肺炎的方法，包括使用输入/输出接口设备从患者护理者处获得患者的两个或更多个诊断参数的值。 该方法包括使用耦合到输入/输出接口的处理器，将两个或更多个诊断参数应用于存储多个预编译的肺炎诊断模型的电子存储器，以识别用于做出诊断的最佳诊断模型。 将两个或多个诊断标志的值应用于已识别的最佳诊断模型，以生成诊断输出。 输入/输出接口设备根据诊断输出来操作，以向护理人员指示患者中是否存在肺炎。 护理人员可以使用诊断为患者提供适当的护理。 肺炎诊断模型源自对肺炎阳性和非肺炎受试者的调查。