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Screening for Atrial Fibrillation During Automatic Blood Pressure Measurements

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ABSTRACT Atrial fibrillation (Afib) contributes significantly to overall cardiovascular risk. Widespread screening for Afib in primary care is sometimes performed by palpation, but suffers from low accuracy and is dependent on clinician experience. Algorithms implemented on oscillometric blood pressure devices can detect Afib with high sensitivity and specificity, but information on factors affecting accuracy is scant. Concurrent diagnostic electrocardiogram (ECG) and oscillometry were measured in participants in ECG clinics at two sites. Root mean squared successive difference (RMSSD) and irregularity index (Irrx) were calculated from oscillometric data and used to train logistic regression classifiers. Monte Carlo cross validation with 20 splits was performed to estimate confidence intervals for mean sensitivity and specificity, with various weightings, in the absence or presence of ectopics, and with or without repeated measurements. 707 measurements, including 168 Afib, were collected from 569 participants with mean (standard deviation) age of 63 (16) years. Sensitivity/specificity of RMSSD and Irrx were 0.982/0.908 and 0.986/0.960 respectively when ectopics were included. Excluding ectopics from the data improved specificity by up to 5%. Nevertheless, based on this performance and after accounting for prevalence of Afib in the population aged over 60 years, and estimated costs of healthcare, oscillometric screening for Afib in this age group could return a positive net health-economic benefit.

INDEX TERMS Atrial fibrillation, biomedical signal processing, medical conditions, medical tests, oscillometric blood pressure.

I. INTRODUCTION

Atrial fibrillation (Afib) is a significant contributor to overall cardiovascular risk, including doubling mortality [1]. Prevalence of Afib in people 55 years and over is estimated at 5.5% and approximately doubles for each decade of life from 50 years old [2], but is not accompanied by obvious symptoms in approximately one-third of these people [1].

ECG is widely accepted as the gold-standard in arrhythmia diagnosis [3], [4] but is a relatively expensive screening tool due to the need for specialist training in measurement and interpretation. Screening for Afib in primary care during routine clinical interactions by pulse palpation is recognised as leading to increased detection of new cases [5], [6]. However, it has been shown that palpation as a screening technique suffers from significant variability in sensitivity and specificity depending on the training and experience of clinician [7]. A systematic review (n=2385) concluded that sensitivity is 94% and specificity 72% [8]. In contrast automated techniques of measuring short term heart rate variability from an ECG have demonstrated both sensitivities and specificities above 90% [9], [10]. Nevertheless, measurement of ECG is not a common procedure in primary care. In contrast, blood pressure (BP) is routinely measured and therefore the ability to screen for Afib using automatic BP monitors is attractive because screening would require minimal change to care practices.

Recently, publications have described detection of possible Afib during oscillometric non-invasive blood pressure (NIBP) monitoring, using proprietary algorithms built into two commercial NIBP devices. This literature reports sensitivity/specificity combinations of 96%/83%, 93%/89% and 100%/92% for various devices and measurement

protocols [11], [12]. Kane *et al.* [13] undertook a recent systematic review of the area. In previously reported work by our group, Afib detection algorithms were evaluated for suprasystolic oscillometric waveforms from a third commercially available device and yielded similar results [14].

Although these results are promising, details of the Afib detection algorithms concerned are scant and sensitivity of the performance to design factors and arrhythmias has not been reported.

In this research we investigate factors affecting the identification of Afib from oscillometric waveforms, with the aim of increasing the knowledge available to successfully design and clinically apply Afib detection algorithms for oscillometric devices.

II. METHODS AND PROCEDURES

A. CLINICAL DATA

This study was performed under ethics approval, which was granted by the Auckland District Health Board Ethics Committee. Participants were recruited from patients presenting to the ECG clinic at two Auckland District Health Board sites: Auckland City Hospital and Greenlane Clinical Centre as part of usual care. All patients who agreed to participate in this study were included in the study. After written informed consent, ECG technicians took concurrent measurements of NIBP (Pulsecor CardioScope 2, USCOM, Sydney, Australia) and 12-lead ECG. Although the measurements were performed at the same time, the period of ECG and pulse wave recordings did not necessarily overlap, as the pulse wave reported by the CardioScope is a subset of the overall NIBP measurement. The CardioScope device automatically reports the quality of the pulse wave measured based on the similarity of the morphology of pressure pulses, and if this was indicated as unacceptable, the measurement was repeated and the first result discarded. In order to investigate intra-subject reproducibility, in a subset of successive patients, both ECG and pulse wave measurements were obtained twice, consecutively. Results presented exclude the second measurements unless otherwise noted.

ECG traces were interpreted by Cardiology Registrars blinded to the device results and classified as normal sinus rhythm (S), Afib (A), atrial flutter (F), or other (X). In each case, records were additionally labelled as exhibiting premature ventricular contractions (PVC) and premature atrial contractions (PAC), left or right bundle branch block (LBBB, RBBB), bradycardia (Brady), tachycardia (Tachy), first or second degree AV node block (1AVB, 2AVB), pacemaker (Pace) or junctional ectopics (JE). ECG interpretation was performed blinded to the results of the CardioScope and pulse wave analysis.

The CardioScope measures blood pressure and then records 10 seconds of pulse wave sampled at 200 Hz during a time when the upper arm cuff is inflated to approximately 30 mmHg above the patient's systolic blood pressure, i.e. suprasystolic. This provides a stable baseline, and pulse waves collected resemble intra-arterial brachial pulse waves, as shown in Fig. 1.

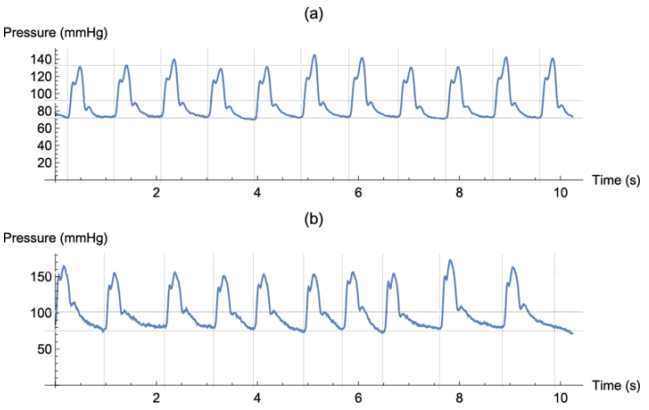

FIGURE 1. Examples of pulse waves collected from patients with (a) sinus rhythm, and (b) atrial fibrillation, as diagnosed from recorded ECGs.

B. FEATURE EXTRACTION AND DATA PROCESSING

In this paper, we collected and calculated features from the CardioScope data that were thought likely to relate to the presence and class of arrhythmias. These are described mathematically in Table 1.

The root mean squared successive difference (RMSSD) and irregularity index (Irrx) are based on the foot-to-foot time from the 10-second suprasystolic pulse waveform, analogous to the interval between R-waves on an ECG. The RR intervals correspond to the intervals between vertical lines shown in Fig. 1. The median RR interval was used to define pulse rate. RMSSD is the standard deviation of differences between successive RR intervals. Irregularity index (Irrx) normalizes the standard deviation of RR intervals by the mean, but ignores RR intervals outside of a specified percentile range. In this work, irregularity index was calculated for the lower percentile ranging from 2.5% to 40%, and upper percentile ranging from 70% to 97.5%.

Ages of participants in subgroups of rhythm class (S or A) and sex were compared using the Mann-Whitney test for difference in mean, and Conover test for difference in variance. Both tests were applied at the 5% significance level.

The receiver operating characteristic (ROC) was used to investigate the performance of the individual features in the binary problem of distinguishing between S and A classes. Area under curve (AUC) was used to quantify baseline performance, variation in performance with changing Irrx parameters, and compare performance when measurements with other identified dysrhythmias (PVC, PAC, LBBB, RBBB, Brady, Tachy, 1AVB, Pace or JE) were included or excluded.

Logistic regression classifiers were trained and validated as follows. In each case 80% of patients were randomly selected to the training set, and the remaining 20% were used for cross-validation. 20 randomisations were applied, and the mean and spread of performance indices are reported. False negative

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TABLE 1. Features for classification.

Feature	Calculation	Parameters
Root Mean Squared Successive Difference	$RMSSD = \sqrt{\frac{1}{N-1}\left(\sum_{i=1}^{N-1}(RR_{i+1} - RR_i)^2\right)}$	RR_i is the i^{th} oscillometric foot-to-foot time interval, N is the number of beats
Signal to Noise Ratio	$SNR = 10\log_{10}\left(\frac{\frac{1}{T}\int_T \bar{p}(t)^2}{\frac{1}{N}\sum_{i=1}^{N}\left(\frac{1}{T}\int_T (p_i(t) - \bar{p}(t))^2\right)}\right)$	$\bar{p}$ is the average of the pressure waveforms for each foot-aligned beat p_i is the i^{th} beat T is the period of a beat N is the number of beats
Irregularity Index	$Irrx\ a-b = \frac{\sigma(RR)}{\overline{RR}} \forall (RR_a < RR < RR_b)$	RR_a and RR_b represent the a^{th} and b^{th} percentile of oscillometric foot-to-foot time interval $\sigma(RR)$ is the standard deviation $\overline{RR}$ is the mean

rate and true positive rate were weighted equally in determining the classification threshold.

Data were analysed using Mathematica version 11.3 (Wolfram Research Inc., Champaign, IL.)

III. RESULTS

569 patients were recruited into the study, with an age (sd) of 63 (16) years and an age range of 15 to 93 years. 235 (41%) of the participants were female. A total of 707 measurements were collected from these participants, and classification of the ECGs is shown in Table 2. A single repeat measurement was taken in 138 patients, from which ECGs were classified differently in one patient, where class changed from S+PVC to A. All measurements were 10 seconds in duration.

TABLE 2. Number of measurements in each class.

Class	# (M/F)	Dysrhythmias								
		PVC	PAC	LBBB	RBBB	Brady	Tachy	1AVB	Pace	JE
S	516 (295/221)	37	25	6	7	6	2	9	9	2
A	168 (110/58)	16	0			2			4	
F	13 (10/3)	0	0							
X	10 (4/6)	1	0						1	

A significant difference in mean age between classes S and A was found. However, there was no significant difference in variance. No difference was found in mean or variance of ages between males and females in either the S or A classes.

Pearson's correlation coefficients between RMSSD and Irrx 25-75, Irrx 25-75 and SNR, and SNR and RMSSD were 0.75, −0.55 and −0.54 respectively.

A. BASELINE CLASSIFICATION PERFORMANCE WITH A SINGLE FEATURE

ROC plots for RMSSD, the negative of SNR, and Irrx 25-75 are shown in Fig. 2. AUC statistics were 0.947 for RMSSD, 0.835 for –SNR and 0.965 for Irrx 25-75. At a sensitivity

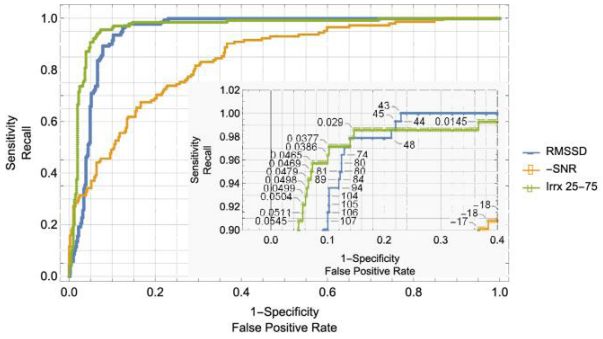

FIGURE 2. ROC plots for measures of pulse variability. Callouts indicate the value of the measure corresponding to the coordiante on the plot.

of 98% which is an average of sensitivities reviewed by Kane [13], the false positive rate and threshold values for RMMSD are 14% and 67 ms, SNR are 74% and 22 dB, Irrx 25-75 are 14% and 0.030.

B. EFFECT OF IRREGULARITY INDEX PARAMETERS ON CLASSIFICATION PERFORMANCE

Irregularity index has two parameters which act to filter out very high and low RR intervals before calculating variability of the remaining intervals. Performance of the binary classifier may be quantified using AUC. Fig. 3 shows a contour plot of AUC with varying parameters.

C. EFFECT OF OTHER ARRHYTHMIAS ON CLASSIFICATION

In the results reported thus far, all A and S class measurements have been used, regardless of the presence of other diagnoses. Fig. 4 illustrates the movement of ROC curves for Irrx 25-75 and RMSSD when including and excluding other identified dysrhythmias (PVC, PAC, LBBB, RBBB, Brady, Tachy, 1AVB, Pace or JE). AUC for Irrx 25-75 improved from 0.965 to 0.979 on removal of other dysrhythmias, and from 0.947 to 0.977 for RMSSD.

D. BINARY CLASSIFICATION BASED ON A SINGLE FEATURE

The results above utilise the full data set to determine the ROC. In clinical practice classifiers would be used to screen new patients to which they had not previously been exposed.

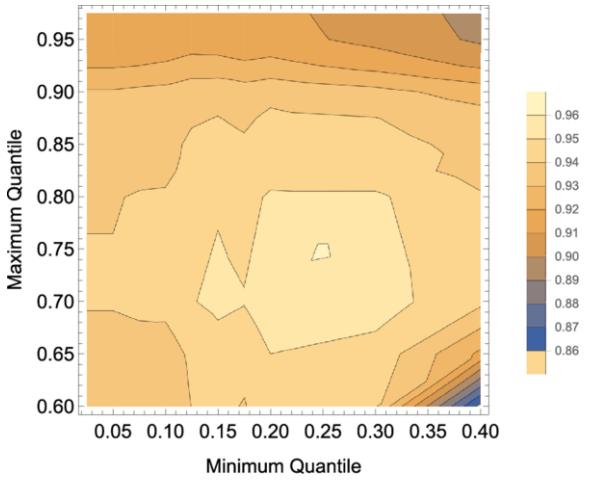

FIGURE 3. **Contour plot showing variation in AUC for Irrx with quantile parameters.**

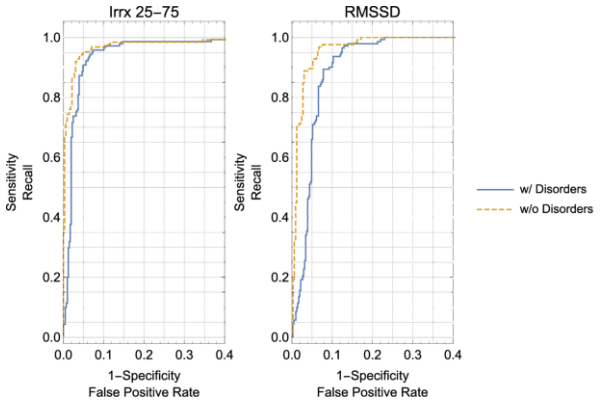

FIGURE 4. **Comparison of ROC when rhythm disorders other than Atrial Fibrillation are included (w/) and excluded (w/o).**

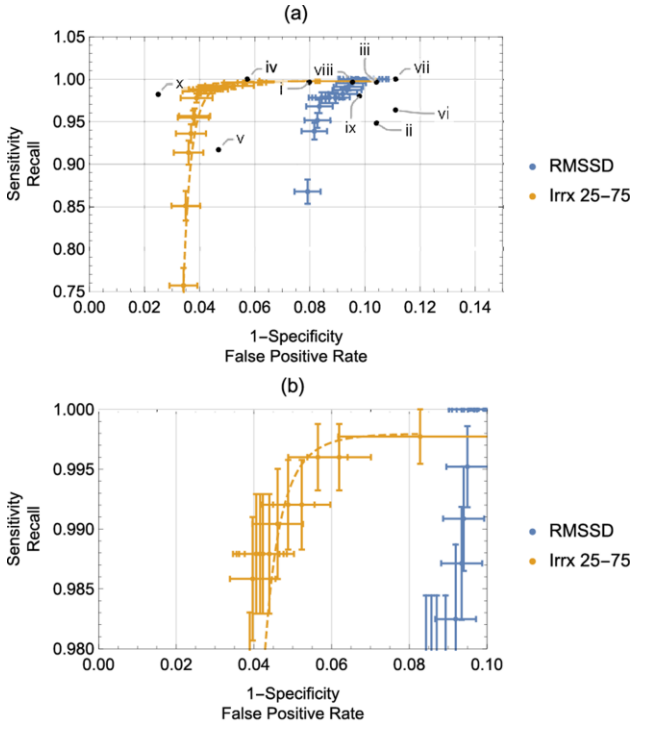

FIGURE 5. **Validation performance of logistic regression classifiers with ectopic (PVC and PAC) beats. Crosses show mean and standard errors for 20-fold cross-validation. Part (b) enlarges a region of (a). Lower case Roman numerals refer to results reported in the literature: i [28], ii [11], iii [25], iv [12], v [12], vi [24], vii [26], viii [27], ix [29] and x [16].**

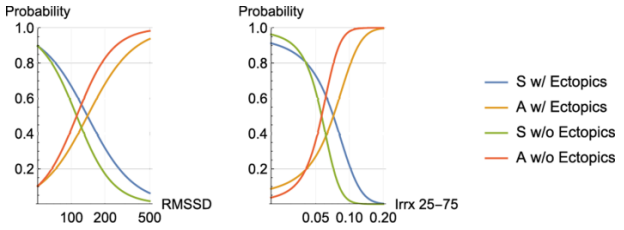

FIGURE 6. **Probability estimates from logistic regression for classification with and without ectopic (PVC and PAC) beats.**

In order to estimate the real-world performance of the metrics, statistical simulation using cross-validation has been employed for 20 randomly selected partitions between training and validation sets. Fig. 5 shows mean±standard errors for False Positive Rate and Sensitivity of logistic-regression classifiers trained with varying weightings for false positive and false negative classification, while keeping all other parameters, training and validation data sets the same. The dashed line is a hand-fitted approximation of the trade-off between sensitivity and specificity, given by

$$sensitivity = 0.998 - \frac{3.72 \times 10^{-12}}{(-0.0179 + FPR)^{6.045}} \qquad (1)$$

where FPR is the false positive rate. The hyperbolic form was chosen as it has asymptotes at high sensitivity and specificity.

Fig. 6 shows examples of probability assignments for logistic regression classifiers based on RMSSD and Irrx 25-75 parameter values with equal cost weighting for false positive and false negative classification.

Classifiers incorporating both RMSSD and Irrx 25-75 as features were also trained and evaluated but showed no significant benefit, which reflects the relatively strong correlation between these features.

E. MULTIPLE MEASUREMENTS

Of the 138 patients who had consecutive measurements, predicted class changed in 10 patients, when using RMSSD as the classifier. Equal numbers of first and second predictions matched the actual classes. When using Irrx 25-75, no differences in prediction were found between consecutive measurements.

IV. DISCUSSION

The cardiology clinic recruitment setting was reflected in the ages of our participants and also prevalence of dysrhythmias. 30% of measurements were classified as exhibiting Afib which is higher than expected for this age group in the general

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population [2]. However, for the estimation of classifier performance, more equal representation of A and S groups is desirable, which is a strength of this study. In S and A groups, the rate of occurrence of PVC was 7.2% and 9.5% respectively. Again, this is higher than could be expected in a more general population (approximately 3%) [15]. PVCs would be apparent in the recorded oscillometric signal, whereas PACs would not. Occurrence of other dysrhythmias in our dataset were insignificant.

ROC plots show a relationship between sensitivity and specificity for a threshold classifier applied to a single independent variable in a known sample. It is apparent from Fig. 2 that SNR is a poor discriminator between S and A classes. However, both RMSSD and Irrx 25-75 show high AUC, with sensitivity and specificity around or above 90%.

Fig. 5 compares performance reported by various studies (as cited in the caption) of Afib screening using oscillometry or pulse wave analysis. Our results are in line with previously reported results, and add information about the trade-off between sensitivity and specificity. Fig. 5 also shows a recent automatic detection algorithm that uses up to 30 sec of ECG (point 'x'). Typically, ECG algorithms achieve higher specificity than oscillometric methods for similar sensitivity regardless of whether they use only RR intervals or include P wave analysis [16]. This indicates limitations in the accuracy of RR intervals estimated from pulse waveforms stemming from an unclear fiducial foot point, and beat-to-beat variation in the duration of isovolumic left ventricular contraction.

In this paper, irregularity index is calculated on the basis of two parameters (the maximum and minimum quantiles). A similar irregularity index is described in Marazzi *et al.* [12] who reports values for thresholds set 25% above and below the mean. Variation in AUC with parameters is presented in Fig. 3, including all dysrhythmias. It is apparent that 25% and 75% quantiles yields the highest AUC. AUC also appears relatively insensitive to these parameters if they are set outside of the range spanning 40% to 60%. This indicates that Irrx is a relatively robust discriminator.

It is apparent from Fig. 4 that performance of both Irrx and RMSSD is degraded by the presence of other rhythm disorders, with RMSSD being more affected. This is expected to be due to the filtering of outliers (heart beats of apparently very short or long duration) in the calculation of Irrx, which does not occur with RMSSD. Therefore, because the presence of ectopic beats is not known in the care environments where oscillometric screening is targeted, Irrx will provide the more robust screening metric. An alternative approach would be to first detect ectopic beats in the oscillometric waveform, similar to methods validated for ECG signals [17]. However, the low number of PVCs make it infeasible to test this approach on our data set.

It is worth noting that outliers may be due to cardiac activity or motion artefact during measurements. Upper-arm cuff-based oscillometric signals are typically more affected by motion than well-adhered ECG electrodes. In our clinical setting, patients were in a quiet clinic room, lying down during measurements and instructed to remain still. Other screening settings may further influence the size and frequency of artefacts, although the SNR measured by the device can be used to help identify when motion artefact is present.

A further suggested mitigation against measurement-to-measurement variability has been to incorporate multiple oscillometric measurements. Stergiou [11] reports using up to three readings, where either one or two classifications of Afib are considered sufficient to diagnose the condition with increased sensitivity or specificity, although the statistical significance of this was not reported. In our subgroup with two consecutive measurements, predicted class was different for the second measurement in 7.2% of patients, and there was no relationship between first or second measurement and actual class. This seems to indicate that repeated measurements in short succession do not contribute any further diagnostic information with the device under test. That is, Afib tends not to appear or disappear over the time of consecutive measurements. Notwithstanding this, it has been shown that continuous ECG measurement over 24 hours, or even six or more months using implantable devices, results in improved detection, particularly of paroxysmal Afib [18]. Although techniques are available that measure continuous pulse waveforms (such as tonometry or volume clamping), they are unsuitable to use for such long periods of time. This research therefore concerns itself with measurements that are quick and minimally disrupt general practitioners' busy workflows.

The use of ROC analysis by itself to predict performance of a classifier is inappropriate. In particular, sensitivity and specificity reported through ROC is calculated with prior knowledge of the full data set. In practice, a classifier must be evaluated based on performance without a-priori knowledge of its subjects. In the work reported here, we use cross-validation to estimate real-world classifier performance, including calculation of confidence intervals for false positive rate (equal to one minus specificity), and sensitivity.

After training logistic regression classifiers, typical probability functions are shown in Fig. 6. It can be seen that Irrx 25-75 provides a somewhat sharper transition between S and A classes, indicating more clear discrimination using this measure. However, for both Irrx and RMSSD there is a shift in probability functions on the inclusion of ectopics in the training set. In both cases, the direction of shifts indicate that the classifiers are confusing ectopics with Afib. As reflected in Fig. 4, ectopics makes classifiers less specific in detecting Afib.

The compromise between sensitivity and specificity was explored further by changing the weightings of utility during classifier training. The relationship between sensitivity and specificity, along with standard errors is shown in Fig. 6. Classification based on Irrx 25-75 has lower false positive rates for sensitivities of up to about 99.5%. However, this difference rapidly disappears at very high sensitivities.

Interestingly, the maximum sensitivity of Irrx 25-75 appears limited to <99.5% on average, with quite large variation in false positive rate for classifiers weighted for higher sensitivities than this, although individual classifiers tested on particular random samples may achieve better results. This limit indicates that about 0.5% of Afib pulse rhythms appear to contain outlier fluctuations that are discarded by the Irrx algorithm. Widening the limits used by Irrx to detect outliers improves specificity but not sensitivity.

The performance of classifiers at these, apparently very high sensitivity levels is important to examine because this tool is expected to be used for screening, and Afib has relatively low prevalence in the population. The probability of detecting new cases of Afib during screening also depends on the expected prevalence of Afib in the part of the population targeted for screening, whether it is present at the time of screening, and whether it is an undiagnosed case. Approximately 6.5% of those aged over 60 years have Afib as diagnosed from a 10-second ECG [2]. Approximately 25% of Afib is paroxysmal in patients known to have Afib [19] and we assume that paroxysmal Afib will not be found by a single measurement [2]. Adjusted overall prevalence is therefore 8.7%. The prevalence of undiagnosed Afib in primary care patients over 60 years is thought to be around 20% [20]. Based on these estimates, assuming that oscillometry is widely used for screening in primary care such that a positive test results in a referral for diagnostic ECG, then the proportions of referred and non-referred patients who actually have Afib are shown in Fig. 7(a) for the Irrx 25-75 architecture; note the logarithmic scale. The relationships are based on the sensitivity-specificity relationship given in (1).

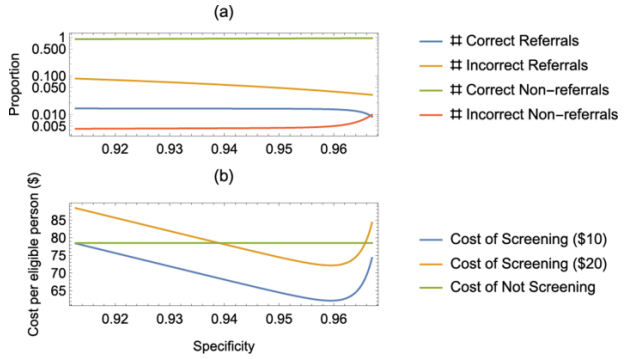

FIGURE 7. Variation with specificity of (a) expected number of correct and incorrect referrals and non-referrals per person in a screening program; and (b) an estimate of the overall cost per person.

It can be seen that the proportion of incorrect referrals (up to 10%) is much higher than the false positive rate for the classifiers found in this study, due to the relatively low prevalence of Afib in the population. Additionally, proportions change significantly for sensitivities greater than 0.96, due to the trade-off between sensitivity and specificity illustrated in Fig. 5.

The health economics of using oscillometry to screen for Afib depends not only on referral rates but also on the cost of screening, treatment and missed diagnoses. These costs are very dependent on characteristics of the implementing healthcare system. Nevertheless, we investigate feasibility and expected behaviour using estimates for cost per person in the screening programme, as follows: Cost of screening, based on primary care clinician time: $10 or $20; cost of referral, based on a diagnostic ECG and cardiologist time: $400; cost of treatment with anticoagulants, and management costs [21]: $720; cost of non-diagnosis [21]–[23] which is the direct cost of stroke, assuming 7% of patients with untreated AFib experience strokes [21]: $60,000. This figure neglects indirect costs associated with stroke. Using these assumptions, the trends in costs per eligible person for screening and not screening are shown for various classifier specificity in Fig. 7(b). There is a range of specificity for which a screening programme may save money by preventing strokes. This range is particularly sensitive to costs of screening and referral; reducing these costs significantly increases tolerance of cost-benefit to lower specificity screening techniques.

V. CONCLUSION

This research has shown the effect of various implementation factors on oscillometric screening of Afib. Given a choice between two common metrics of dysrhythmia, if very high sensitivities are required, RMSSD appears to be a better candidate as maximum Irrx sensitivity for specificity <25% appears to be limited to approximately 99.8%. Below this limit, Irrx generally provides higher specificity for equivalent sensitivity and we have found that the performance of Irrx has been found to be relatively insensitive to choice of parameters near to Irrx 25-75. Careful consideration needs to be given to the prevalence of dysrhythmias other than Afib in the screening population, as these have been found to degrade specificity by up to 5%, whereas sensitivity of Irrx (but not RMSSD) is unaffected. Repeated consecutive measurements do not seem to contribute to classifier performance in well-collected data.

This research contributes information to guide the adoption of oscillometric or other pulse-wave methods to screen for Afib, including the effect of real-world factors that affect the performance of the classifiers, and confidence intervals for sensitivity and specificity.

The health economics of oscillometric screening will depend on both policy, clinical and technological choices. Still, it appears feasible that such screening programmes could yield positive net benefit from a health-economics perspective, with currently achievable classifier performance.

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