Thorax

Tablet and web-based audiometry to screen for hearing loss in adults with cystic fibrosis

Journal:	*Thorax*
Manuscript ID	thoraxjnl-2019-214177.R2
Article Type:	Original research
Date Submitted by the Author:	n/a

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Keywords:	Cystic Fibrosis, Systemic disease and lungs, Respiratory Infection

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Tablet and web-based audiometry to screen for hearing loss in adults with cystic fibrosis

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Word count: 3575

Key messages:

Key question:
Can tablet or web-based audiometry be used to screen for hearing loss in adults with Cystic Fibrosis?

What is the bottom line:
Tablet-based audiometry performed by non-audiologists in an outpatient setting can accurately screen for hearing loss in chronic lung disease.

Why read on?
This study proposes an integrated ototoxicity monitoring programme using tablet-based audiometry to monitor the under-recognised high prevalence of hearing loss in individuals with chronic lung disease.

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ABSTRACT:

Introduction:

Individuals with chronic lung disease (e.g. Cystic Fibrosis (CF)) often receive antimicrobial therapy including aminoglycosides resulting in ototoxicity. Extended high-frequency audiometry has increased sensitivity for ototoxicity detection, but diagnostic audiometry in a sound-booth is costly, time-consuming and requires a trained audiologist. This cross-sectional study analysed tablet-based audiometry (Shoebox MD) performed by non-audiologists in an outpatient setting, alongside home web-based audiometry (3D Tune-In) to screen for hearing loss in adults with CF.

Methods:

Hearing was analysed in 126 CF adults using validated questionnaires, a web self-hearing test (0.5-4kHz), tablet (0.25-12kHz) and sound-booth audiometry (0.25-12kHz). A threshold of ≥25dB hearing loss at ≥1 audiometric frequency was considered abnormal. Demographics and mitochondrial DNA sequencing were used to analyse risk factors, and accuracy and usability of hearing tests determined.

Results:

Prevalence of hearing loss within any frequency band tested was 48%. Multivariate analysis showed age (OR–1.127;(95%CI:1.07–1.18;p-value<0.0001) per year older) and total intravenous antibiotic days over 10 years (OR-1.006;(95%CI:1.002-1.010;p-value=0.004) per further IV day) were significantly associated with increased risk of hearing loss. Tablet audiometry had good usability, was 93% sensitive, 88% specific with 94% negative predictive value to screen for hearing loss compared to web self-test audiometry and questionnaires which had poor sensitivity (17% and 13% respectively). Intra-class correlation of tablet versus sound-booth audiometry showed high correlation (ICC>0.9) at all frequencies ≥4kHz.

Conclusions:

Adults with CF have a high prevalence of drug-related hearing loss and tablet-based audiometry can be a practical, accurate screening tool within integrated ototoxicity monitoring programmes for early detection.

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1. INTRODUCTION

Individuals with chronic lung disease such as bronchiectasis, Cystic Fibrosis (CF) and Chronic Obstructive Pulmonary Disease (COPD) are prone to life-threatening infections with gram-negative bacteria such as *Pseudomonas aeruginosa*.[1] This often necessitates repeated aminoglycoside antimicrobial therapy, which remain primary agents of choice, with potential ototoxic (cochlea/vestibulotoxicity) side effects, resulting in permanent high-frequency sensorineural hearing loss.[2] Furthermore, macrolides, used widely in chronic lung disease as immunomodulatory or antimicrobial therapy and prolonged intravenous amikacin for non-tuberculous mycobacteria and multi-drug resistant tuberculosis (MDR-TB) treatment have potential for significant ototoxicity.[3-8]

Despite widespread ototoxic antimicrobial therapy use in chronic lung disease, implementation of national and international ototoxicity monitoring recommendations in the United Kingdom is sparce and inconsistent.[9] Within CF, there are a number of studies detailing prevalence of hearing loss through pure-tone audiometry, with rates of ~40-56% in adults.[10] When controlling for age, cumulative lifetime intravenous aminoglycoside dosing, had a significant negative effect on hearing.[10] Several variants in the mitochondrial 12S ribosomal rRNA gene are additionally associated with aminoglycoside-induced hearing loss, the most common being m.1555A>G.[11-12] There is, however, little data on prevalence of these variants in adult chronic lung disease and effectiveness of genomic screening to identify high-risk individuals.[13]

Despite a high prevalence of ototoxicity in CF, developing effective ototoxicity monitoring programmes (OMPs) has been problematic. A recent study has highlighted the challenges of OMP implementation in chronic lung disease, with audiology departments often not co-located with respiratory services, hence necessitating further outpatient visits with delay and poor attendance.[14]. Sound-booth audiometry is costly, time and labour-intensive and impractical in large cohorts on a frequent basis. This is particularly pertinent within resource-poor countries, where ototoxic effects are even more prevalent and reported in >60% of patients receiving aminoglycoside-containing MDR-TB antimicrobial regimens.[15] Furthermore, extended high-frequency audiometry, which is more sensitive in detecting early ototoxic effects, is often not routinely performed.[16]

There has hence been a technology drive to enable tablet, smartphone or web-based OMPs integrated within the clinical service to streamline care. Recent studies have validated this technology in healthy children and adults, but to date, there are no studies validating their use to detect hearing loss in adults with chronic lung disease.[17-19] In this multicentre cross-sectional study, we analyse the accuracy of tablet and web-based audiometry performed by non-audiologists in an outpatient setting as screening tools for hearing loss in adults with CF and determine risk factors for hearing loss. We additionally sequence the MT-*RNR1* gene to analyse prevalence and association of known variants with hearing loss.

2. METHODS

2.1 Participants

Study materials and protocols were approved by the South-Central Research Ethics Committee (REC reference: 18/SC/0057) with informed written consent obtained at participant's clinic visit or inpatient stay. 156 patients were

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recruited to the study from Royal Brompton and Harefield (RBH) and Kings College Hospitals (KCH) NHS Foundation Trusts CF departments with 126 adults completing study follow-up. Exclusion criteria were pre-existing hearing impairment requiring hearing aids. Clinical demographics were obtained from electronic health records (EHRs) and the UK CF Registry.[20] Total intravenous (IV) antibiotic days over the last 10 years was collected from UK CF Registry and cumulative intravenous antimicrobial dosing for aminoglycosides, available for preceding 5 years, from EHRs. See supplementary data.

2.2 Procedures

Following recruitment, participants completed a web-based hearing test (developed within the 3D Tune-In project, (http://3d-tune-in.eu/)) on any personal computer with standard earphones/headphones.[21] For test usability and speed, pure-tone air conduction audiometry at only 3 frequencies was tested: 0.5, 1, 4kHz. Test time was ~10 minutes.

Subsequently, during outpatient or inpatient setting, participants completed tablet-based audiometry (SHOEBOX® Audiometry, Shoebox Ltd) with a non-audiologist research fellow using calibrated RadioEar DD450 circumaural headphones. Following otoscopy to ensure a clear ear canal and visible tympanic membrane, pure-tone air conduction audiometry at 0.25, 0.5, 1, 2, 4, 6, 8, 10, 12.5kHz was performed. Due to the cross-sectional nature of the study alongside the median age of the adult CF cohorts with a significant number >40 years old where measurable hearing thresholds >12.5kHz would be unlikely, extended high frequency audiometric testing was pragmatically limited to ≤12.5kHz for tablet and formal audiometry. in whom . Background noise was monitored by the device and testing halted until below an accepted level. Test time was ~10-15 minutes.

Lastly, sound-attenuated booth audiometric testing was completed at an audiology clinic (Imperial College Healthcare NHS Trust or Guys and St. Thomas' Hospitals' NHS Foundation Trust) using standard equipment: 1)Pure-tone air conduction audiometry at 0.25, 0.5, 1, 2, 4, 6, 8, 10, 12.5kHz (matching tablet audiometry) 2)Pure-tone bone conduction audiometry from 0.5–4kHz. Test time ~15-20minutes. A threshold of >25dB hearing loss at ≥1 audiometric frequencies was considered outside normal hearing range as per current National Guidelines for Classification of Hearing Loss.[22] Conductive hearing loss was defined as the presence of an air-bone gap exceeding 10dB air-bone gap over three of the following frequencies 500, 1000, 2000, 3000 or 4000Hz. See supplementary data.

Study participants additionally completed validated questionnaires to evaluate the impact of hearing loss on everyday tasks (Hearing Handicap Inventory for Adults (HHIA))[23], vestibular toxicity (Vertigo Handicap Questionnaire)[24]; and tinnitus (Tinnitus handicap questionnaire).[25]

2.3 Patient experience and usability analysis

To evaluate test usability, three standardised scales were applied to evaluate user experience and perceived usability: the User Experience Questionnaire (UEQ);[26] the Usability Metric for User Experience (UMUX);[27] and the Net Promoter Score (NPS).[28-29] See supplementary data.

2.4 Mitochondrial SNP analysis

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DNA was extracted from EDTA blood samples from 124 study participants. Sequencing of the MT-*RNR1* gene was performed by PCR and Sanger sequencing of the two overlapping fragments spanning the entire gene. Results were visualised using Unipro UGENE 1.32 and sequences mapped to the reference mtDNA genome (NC_012920.1).[30] All sequence variants observed in patient samples within the sequenced region were recorded. See supplementary data.

2.5 Statistical analysis

Results were presented as mean±standard deviation, median and interquartile range if non-parametric or percentage if appropriate. Univariate logistic models were fitted for each of the covariates of interest, including the allele frequency of each of the observed mtDNA variants. Univariate analysis was performed for each covariate of interest, and variables with p-values<0.2 were used in the multivariate model. A stepwise selection method was used to obtain the best combination of variables. Multivariate models were fitted using the variable age as continuous. Time interaction of IV antibiotic use was modelled by creating a weighted score as the sum of (1/*x* years-ago)*number of IV days *x* years ago. Sensitivity, specificity, positive and negative predictive values were used to analyse accuracy of tablet and web-based audiometry using sound-booth audiometry as gold-standard. Intraclass correlation and Bland-Altmann plots were used to determine reliability of tablet-based audiometry compared to sound-booth audiometry. Monte Carlo simulation was used to compare cost-efficiency of different screening strategies (see supplementary data). For usability analysis, reliability of the scales were estimated using Cronbach's Alpha and paired t-test used to analyse differences between tablet, web and formal sound-booth audiometry. P values<0.05 were deemed significant.

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3. RESULTS

Overall prevalence of hearing loss in our cohort at any frequency band tested through sound-booth audiometry was 45% (n=57). Hearing loss was predominantly sensorineural with only 5% of abnormal hearing due a conductive defect (n=3) and a further 9% (n=5) having a mixed pathology. The median age of our cohort was 31.5 (IQR–24-42) (Figure 1). Similar to previous studies, the majority of hearing loss was at higher frequencies (≥8kHz), however, significant hearing loss was seen across all frequencies (Figure 1B). A breakdown of hearing loss by frequency range is shown in Supplementary Figure 1A. To determine effect on quality-of-life, thresholds were averaged across frequencies critical for speech recognition/development (0.5-4kHz). 10 (8%) of our cohort had abnormal average thresholds in this range (Figure 1C), suggesting likely significant impact on quality-of-life. Supplementary Table 1 shows demographics associated with study subjects with abnormal average thresholds critical for speech recognition/development (0.5-4kHz). Supplementary Figure 1B compares hearing in the 20-29 year old subjects in our adult CF cohort to comparable data from a large recent study of hearing in a normal healthy population.[31] This shows significantly increased average thresholds at 1, 2, 4 and 8kHz in our CF cohort at an age where presbyacusis is unlikely.

Table 1 presents cohort clinical demographics alongside univariate association with hearing loss. Maintenance azithromycin use, age, forced expiratory volume in 1 second (FEV1), and total IV antibiotic days over preceding 10 years were associated with increased hearing loss. Within multivariate analysis, only age and total IV antibiotic days in the preceding 10 years were significantly associated with hearing loss, with covariate age explaining most of the heterogeneity in the model. For each year older the probability of an abnormal sound-booth audiometry test increases **12.8%** (OR-1.127; 95%CI:1.074-1.182; p-value<0.0001). Despite adjustment for age, for each extra IV antibiotic day, the probability of an abnormal audiometry test increases **0.6%** (OR-1.006; 95%CI:1.002-1.010; p-value=0.004), representing a **6.7%** (OR-1.067; 95%CI:1.028-1.966) increased probability following a standard 14-day IV antibiotic course. The association, however, is predominantly driven by outliers with hearing loss and high historical IV antibiotic use, with similar average total IV antibiotic days over 10 years in those with and without hearing loss. Multivariate analysis to determine the effect of time of IV antibiotic use was performed by creating a weighted score as the sum of (1/*x* years-ago)*number of IV days *x* years ago. This revealed a significant time effect of IV antibiotic administration on ototoxicity (p-value - 0.0043; OR-1.015 (95%CI:1.005-1.026).

Analysis of total IV Tobramycin doses over the preceding 5 years revealed a trend towards reduced administration in those with abnormal hearing loss. This reflects a number of subjects not receiving IV aminoglycosides in this time-period due to known pre-existing hearing loss. Hearing questionnaire scores were not significantly associated with hearing loss. Prevalence of significant vestibular toxicity and tinnitus symptoms were 9.5% and 7.1% respectively which is far greater than the expected UK prevalence, but was not significantly associated with hearing loss.[32] Multivariate analysis again revealed age (p value=0.038; OR-1.063; 95%CI:1.003-1.227) and total IV antibiotics over 10 years (p=0.004; OR-1.118; 95%CI:1.037-1.205) were significantly associated with tinnitus. No variables were significantly associated with vestibular toxicity within multivariate analysis.

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Table 1 - Clinical demographics of study cohort and univariate association with abnormal sound-booth audiometry

	All (n=126)	Normal sound-booth audiometry (n=69)	Abnormal sound-booth audiometry (n=57)	P-value univariate analysis
Sex ((n (%) female)	52 (41.3)	27 (39.1)	25 (43.8)	0.59
Chronic *Pseudomonas aeruginosa* colonisation (n (%))	74 (58.7)	44 (63.8)	30 (52.6)	0.46
Previous history of fungal disease treatment (n (%))ǂ	49 (38.9)	31 (44.9)	18 (31.9)	0.13
Previous history of non-tuberculous mycobacterial treatment (n (%))ǂ	25 (19.8)	15 (21.7)	10 (17.5)	0.56
Pancreatic insufficiency (n (%))	114 (90.5)	64 (92.8)	50 (87.7)	0.34
Chronic rhinosinusitis (n (%))	41 (32.5)	19 (27.5)	22 (38.6)	0.19
eGFR (%>90) (n (%))	90 (71.4)	54 (78.2)	36 (63.2)	0.05
Maintenance azithromycin (%Yes)	80 (63.5)	38 (55.1)	42 (73.7)	**0.03**
HHIA Score (n (%) abnormal)	14 (11.1)	7 (10.1)	7 (12.3)	0.70
Tinnitus Score (n (%) abnormal)	12 (9.5)	6 (8.7)	6 (10.5)	0.73
Dizziness Score (n (%) abnormal)	9 (7.1)	6 (8.7)	3 (5.3)	0.46
Age (median (IQR))	31.5 (24-42)	30 (24-34)	42 (29-49)	**<0.0001**
FEV1 (median (IQR))	2.1 (1.54-2.92)	2.56 (1.7-3.07)	1.85 (1.39-2.75)	**0.008**
FEV1 %predicted (median (IQR))	62 (46-80)	72 (51-82)	61 (46-73)	0.17
BMI (median (IQR))	22 (20.1-23.8)	21.5 (20-22.6)	22.3 (20.4 - 24.6)	0.07
Total days of intravenous antibiotics in past 10 years (median (IQR))	56 (21-154)	56 (28-119)	56 (28-182)	**0.03**
***Total doses intravenous tobramycin (median (IQR))**	28 (6-75)	28 (3-111)	28 (7-66.5)	0.08
***Total doses inhaled tobramycin (median (IQR))**	224 (0-2240)	56 (0-1344)	938 (0-3001)	0.07
***Intravenous amikacin (binary) %**	17.5	17.9	16.4	0.47

*Retrospective antimicrobial prescribing data only available in n=114 for preceding 5 years through electronic health records.

ǂ Includes any treatment post CF diagnosis.

HHIA – Hearing Handicap Inventory for Adults; eGFR – estimated Glomerular Filtration Rate; FEV1 – Forced expiratory volume in 1 second; BMI – Body mass index; IQR – Interquartile range;

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Given the study analysed extended high-frequency audiometry within an adult cohort where age-related hearing loss (presbycusis) is a possible aetiology, we further explored the effect of age on hearing. Figure 1D provides a graphic cohort age representation with a significant proportion (33%) of individuals ≥40 years, where presbycusis may account for hearing loss.[31] The study cohort is representative of the total adult CF cohort at the Royal Brompton adult CF centre, which has a median age of 32 (range 16-80). Figure 2A is a density plot showing the association between age and hearing loss with a gradual increase in hearing loss prevalence as age approaches 40. Using a multivariate model with age as a binary variable with ≥40 as a cut-off, the odds ratio of abnormal hearing in individuals with CF ≥40 compared to <40 years old is **28.6** (CI:8.3-100). Although age is clearly a significant factor in hearing loss development, prevalence of hearing loss in individuals <40 years was still high (28.6%). 50% of individuals with abnormal average thresholds in speech discriminatory frequencies (0.5-4kHz) were again under 40 years (4% of total cohort). Figure 2B is a density plot showing the association between total IV antibiotic days over the preceding 10 years and hearing loss. Although significant within multivariate modelling, there is no clear cut-off useful for screening purpose.

Forty-two different mtDNA variants in the sequenced MT-*RNR1* gene region were observed in our cohort. Thirty-seven variants were single nucleotide variants (SNPs), whereas five were small indels (Supplementary Table 2). No m.1555A>G variants were detected, but the known mt variant m.827A>G, previously associated with aminoglycoside ototoxicity, was found in a single individual with normal hearing, despite previous aminoglycoside exposure.[33] Six novel mtDNA variants were observed, of which two variants, m.489T>C (rs28625645) and m.1719G>A (rs3928305) showed significant differences in allele frequency between individuals with normal and abnormal hearing. The m.489T>C variant was significantly more frequent in individuals with normal hearing, while the m.1719G>A variant was present at the expected population allele frequency in individuals with normal hearing (2.99%), but was more common in those with abnormal hearing (14.04%, p=0.043).

Table 2 shows the accuracy of tablet and web-based audiometry and HHIA questionnaire to detect hearing loss using sound-booth audiometry as gold-standard. Tablet audiometry showed high negative predictive value in screening for hearing loss with additional good sensitivity, specificity and positive predictive value. In contrast, although web-based audiometry had high specificity, given the limited frequencies tested, had poor sensitivity and negative predictive value. Similarly, HHIA questionnaire had high specificity but poor sensitivity and negative predictive value. Given the significant effect of age on hearing loss, we performed a Monte Carlo simulation to compare the cost-efficiency between universal screening with sound-booth or tablet audiometry or limiting tablet audiometry screening to adults <40 years old given the increased probability of hearing loss above that age. Universal sound-booth audiometry screening in a sample cohort (n=539) would cost £80,850. Universal tablet-audiometry screening would cost on average £39,605 (95% CI: 34,550-45,050). Limited tablet screening to adults <40 years old would cost on average £45611 (95% CI: 41,300-50,450). Universal tablet audiometry screening appears to be the most cost-efficient because of the true negative patients ≥40 years-old that could avoid sound-booth audiometry testing, in whom there would be an added socio-economic benefit with reduced outpatient visit requirement.

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Table 2 – Accuracy of tablet and web-based audiometry and validated symptom questionnaire (HHIA) to detect hearing loss in study cohort.

	Tablet audiometry	Web-based audiometry	HHIA Questionnaire
Apparent prevalence	0.48 (0.39-0.57)	0.07 (0.03-0.12)	0.11 (0.06-0.18)
True prevalence	0.45 (0.39-0.54)	0.45 (0.37-0.55)	0.45 (0.36-0.54)
Sensitivity	0.93 (0.83-0.98)	0.14 (0.06-0.26)	0.12 (0.05-0.24)
Specificity	0.88 (0.78-0.95)	1.00 (0.95-1.00)	0.90 (0.80-0.96)
Positive predictive value	0.87 (0.76-0.94)	1.00 (0.63-1.00)	0.50 (0.23-0.77)
Negative predictive value	0.94 (0.85-0.98)	0.58 (0.49-0.67)	0.55 (0.45-0.65)

95% confidence intervals shown in brackets

Intraclass correlation and Bland-Altmann plots were used to further analyse tablet-based audiometry reliability compared to sound-booth audiometry. Figure 3 illustrates the high correlation (>0.9) between tablet and sound-booth audiometry at all frequencies ≥4kHz where most of the hearing loss was found. Reliability reduced at lower frequencies likely because of the effects of background noise. Representative Bland-Altmann plots are shown in Supplementary Figure 2.

Figure 4 and Supplementary Table 3 shows usability analysis of sound-booth, tablet and web-based audiometry. Tablet audiometry seems equivalent to sound-booth audiometry in terms of perceived usability (UMUX = 78, B+) but better in terms of intention-to-use and promote (NPS = +68). Although, web-based audiometry appears an acceptable solution (UMUX = 72, C+) with a positive intention to promote (NPS = +11), it is less satisfactory than the others and is outperformed by sound-booth audiometry (UMUX = 77.5, B+; NPS = +62). The UEQ results confirm this and conversely show sound-booth and tablet-based audiometry provides a similar experience of use. Although sound-booth audiometry seems more dependable to end-users, it appears less acceptable in terms of stimulation and novelty compared to tablet audiometry. Analysis also highlights a tendency of users to prefer tablet audiometry in terms of intention-to-promote compared to sound-booth testing.

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4. DISCUSSION

Our study similar to those previously reported, highlights a significant prevalence of sensorineural hearing loss (48%) in adults with CF, with a proportion of individuals (8% of study cohort) with severe hearing loss in frequency ranges that will affect speech discrimination and quality of life.[10] Studies have highlighted the cognitive implication and effect on quality-of-life from severe ototoxicity related sensorineural hearing loss in children.[34-36] To the authors' knowledge, despite the high prevalence in adults with chronic lung disease, no studies evaluating the effect of ototoxicity on quality-of-life have been performed.

Our data reconfirms the evidence for routine hearing evaluations with extended high frequency (>8kHz) to detect early ototoxicity. As previously shown, age is a significant factor in determining likelihood of sensorineural hearing loss, particularly in individuals >40 years old. This is in line with previous studies reporting increased ototoxicity in older patients receiving aminoglycosides both with and without CF.[10, 37] Sensorineural hearing loss was, however, seen in a relatively large percentage of individuals <40 years old with a proportion again having severe hearing impairment. Age itself is a known risk factor for hearing loss through presbycusis, but within the study cohort, also represents likely cumulative antimicrobial therapy.

The total number of IV antibiotic days in the preceding ten years was associated with increased risk of hearing loss, but with no clear cut off useful for screening purpose. Lifetime cumulative aminoglycoside exposure is known to be associated with greater odds of developing sensorineural hearing loss.[10] This study evaluated whether retrospective antimicrobial prescribing data easily accessible through national registry or EHRs would be useful for screening/stratification purpose, and highlights the significant limitations in available data. UK CF Registry data does not record individual aminoglycoside or antimicrobial dosing. Hence, although cumulative IV antibiotic days in the last 10 years was significantly associated with an increased likelihood of hearing loss in multivariate modelling, the association is relatively weak with no clear cut-off for screening purpose. Furthermore, in the centres in our study, retrospective EHR prescribing data was only available for 5 years. In an adult cohort with a median age of 31 years, this does not accurately represent cumulative life-time aminoglycoside exposure, and hence was not useful for screening stratification. In fact, given the likelihood of aminoglycoside avoidance in subjects with pre-existing confirmed hearing loss, there was a trend towards decreased aminoglycoside administration in subjects with hearing loss. Although archived information is often available, this is impractical in a clinical setting. If accurate, longer-term retrospective antimicrobial dosing is easily accessible through EHRs this may potentially enable future screening stratification through aminoglycoside exposure.

Our study also highlights the limitations in mtDNA variant genomic screening of in CF. In 124 adults, no m.1555A>G variants were identified, however, given an estimated population frequency of 0.26%, this is unsurprising.[12] The high overall prevalence of hearing loss, combined with a low prevalence of known mtDNA variants with increased risk of aminoglycoside-related hearing loss and reports of incomplete penetrance, suggest that mtDNA screening currently may not be cost-effective or additive to a comprehensive OMP in an adult setting.[13, 38] Our findings of two novel mitochondrial variants, one significantly associated with hearing loss, and the other apparently protective require

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confirmation in larger studies given the inability to correct for multiple testing in univariate analysis with this cohort size.

Key to preventing disabling hearing loss is an ability to perform efficient audiometric monitoring and early ototoxicity identification to enable an antimicrobial prescribing change if possible. The emergence of novel otoregenerative compounds currently in clinical trials highlight the importance for future therapeutic strategy.[39] Our study shows the potential applicability of tablet-based audiometry to accurately screen for hearing loss in adults with CF with high sensitivity, specificity and negative predictive value. The approximate tariff for a formal audiogram in the UK NHS is ~£150. As shown in our health-economic modelling, universal formal sound-booth audiometry in a cohort of ~500 individuals would cost ~£80000/year. In comparison, the current annual cost of universal tablet-based audiometry is modelled to be ~£40000/year which represents a significant healthcare cost saving. The use of tablet audiometry in an outpatient setting by non-audiologists can enable streamlined OMP clinical integration with high uptake. The good end-user usability of the device reinforces likely successful clinical care pathway integration, with a high negative predictive value enabling concentration of audiology time/expertise on high-risk individuals increasing pathway efficiency. Evaluation of real-world clinical integration including further health-economic analysis will be necessary, however, to fully determine impact. Applicability in other chronic lung disease cohorts with increased median age and resource-poor regions also requires evaluation, however, studies in older healthy individuals suggest translatability.[40]

Our study highlight the limitations of home web-based testing using off-the-shelf earphones, in uncontrolled (i.e. potentially noisy) environments at limited frequencies (i.e. speech discrimination range). Although highly specific, web-based testing had poor sensitivity in identifying hearing loss. To enable future home testing accessibility, the development of low-cost insert earphones suitable for extended high-frequency audiometry may increase reliability.[41] Additionally, although useful for quality-of-life assessment, HHIA questionnaires were not sensitive or accurate in detecting hearing loss. The false positive incidence possibly suggests abnormal auditory processing in these subjects however further research is required to understand the use of validated questionnaires as screening tools in adult cystic fibrosis.

A limitation of our study is its cross-sectional design, given the primary outcome was to evaluate accuracy and usability of tablet/web-based audiometry compared to sound-booth audiometry. An obvious potential benefit to tablet-based audiometry, however, is an easier ability to longitudinally monitor individuals with increased ototoxicity risk. Recent studies have highlighted the ototoxic potential of a single course of aminoglycosides in CF.[42] This was highlighted during our study where tablet based audiometry accurately identified early ototoxicity, enabling antimicrobial therapy change following shared decision making (Supplementary Figure 3). Further evaluation of longitudinal tablet audiometry monitoring including at increased extended high frequency up to 16kHz within an integrated OMP is required, but the high reliability compared to sound-booth audiometry in our study is promising. A further limitation of the study due its cross-sectional design, is the possibility of transient hearing loss detection given a small number of patients were tested whilst on IV antibiotics. Overall study hearing loss prevalence is however similar to the published literature. Lastly, given the size of the cohort we did not account for the effect of multiple testing within univariate and multivariate modelling.

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Given our results, we propose an algorithm for incorporating tablet-based audiometry within an integrated OMP, using annual screening including vestibular and tinnitus questionnaires to identify individuals requiring sound-booth audiometry and evidence of ototoxicity. Tablet-based audiometry is subsequently used for longitudinal monitoring, with threshold shift modified from American Speech-Language Hearing Association guidelines used to identify ototoxic change ((i)a 15dB threshold shift in (at least) one frequency OR (ii)a 10dB threshold shift in two consecutive (adjacent) test frequencies), with testing frequency dependent on ongoing potential ototoxic medication use (Figure 5). Further evaluation following implementation is required to determine effectiveness.

In summary, our study highlights the significant ototoxic impact of antimicrobial prescribing in adults with CF, and presents data highlighting the applicability of tablet-based audiometry as a practical screening tool with high accuracy that can be used within integrated ototoxicity monitoring programmes in chronic lung disease to identify ototoxicity at an early stage.

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Acknowledgements:

The authors would like to thank the Audiology departments at Imperial College Healthcare NHS Trust and Guy's and St. Thomas' NHS Foundation Trust for their support through the study. Additionally thanks to Sam Wilkinson, Lorna Briggs, Charlotte Powell and Marylka Griffiths in the Clinical Genetics and Genomics laboratory, Royal Brompton and Harefield NHS Foundation Trust, London, UK for technical assistance with mitochondrial DNA analysis.

Funding: This study was funded through a Clinical Innovation and Excellence award from the UK Cystic Fibrosis Trust and the NHS Darzi Fellowship in Clinical Leadership programme. Alberto Vidal-Diez and Melody Ni received funding from the National Institute of Health Research (NIHR). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

Competing interests: AS has received grant funding from Vertex Pharmaceuticals and Gilead Sciences and received personal fees for lecturing from Gilead Sciences. NJS has received personal fees for consultancy and lecturing from Vertex, Teva and Zambon Pharmaceuticals, Chiesi Ltd, Novartis International, Pulmocide Ltd, Roche and Gilead Sciences. CE has received personal fees for consultancy and lecturing from Gilead Sciences, Teva and Zambon pharmaceuticals.

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Figure legends

Figure 1: A) Graph showing overall prevalence of hearing loss detected by formal sound-booth audiometry in study cohort with predominant abnormality in extended high frequencies. **B)** Scatter plot showing individual thresholds for study subjects at each frequency through sound-booth audiometry to illustrate severity. Dotted red line represents cut-off for abnormality (≥25dB). **C)** Graph showing average thresholds within speech discriminatory frequencies (0.5-4kHz) through sound-booth audiometry for study subjects. Dotted red line again represents cut-off for abnormality (≥25dB). **D)** Bar chart representing age breakdown of study cohort and highlighting significant proportion of individuals over 40 years old.

Figure 2: A) Density plot showing association between age and abnormal hearing in study cohort. Peak prevalence in hearing loss is seen in subjects over 40 years old. **B)** Density plot showing association between total intravenous antibiotic days over the preceding 10 years and hearing loss. No clear cut-off is seen which would be useful for screening stratification.

Figure 3: Intraclass correlation (ICC) analysis between tablet and sound-booth audiometry

Figure 4: Graphic representation of User Experience Questionnaire (UEQ) results of **A)** Sound booth **B)** Tablet-based and **C)** Web-based audiometry. Results show that web-based audiometry is less appreciated with low levels of attractiveness, dependability, stimulation and novelty. Conversely, sound booth and tablet-based audiometry seem to provide a similar experience of use. **D)** Comparative analysis of the experience (UEQ) in performing tablet-based audiometry or formal sound booth audiometry. (** - $P<0.01$; ns – not significant)

Figure 5: Proposed algorithm for an ototoxicity monitoring programme incorporating tablet-based audiometry integrated within clinical care in adults with CF.

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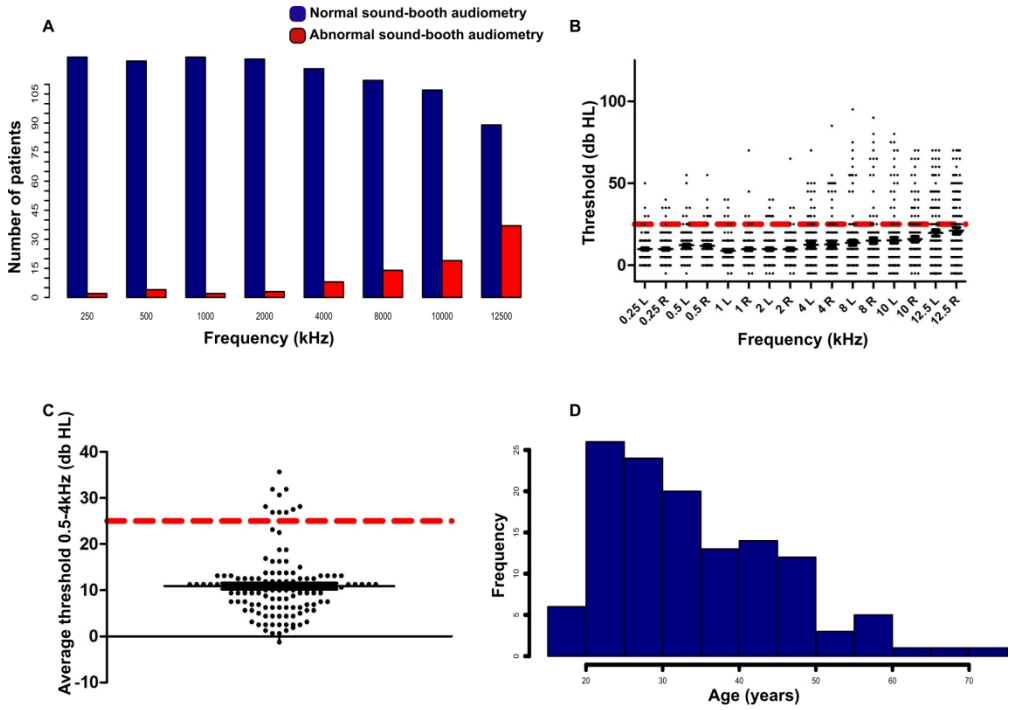


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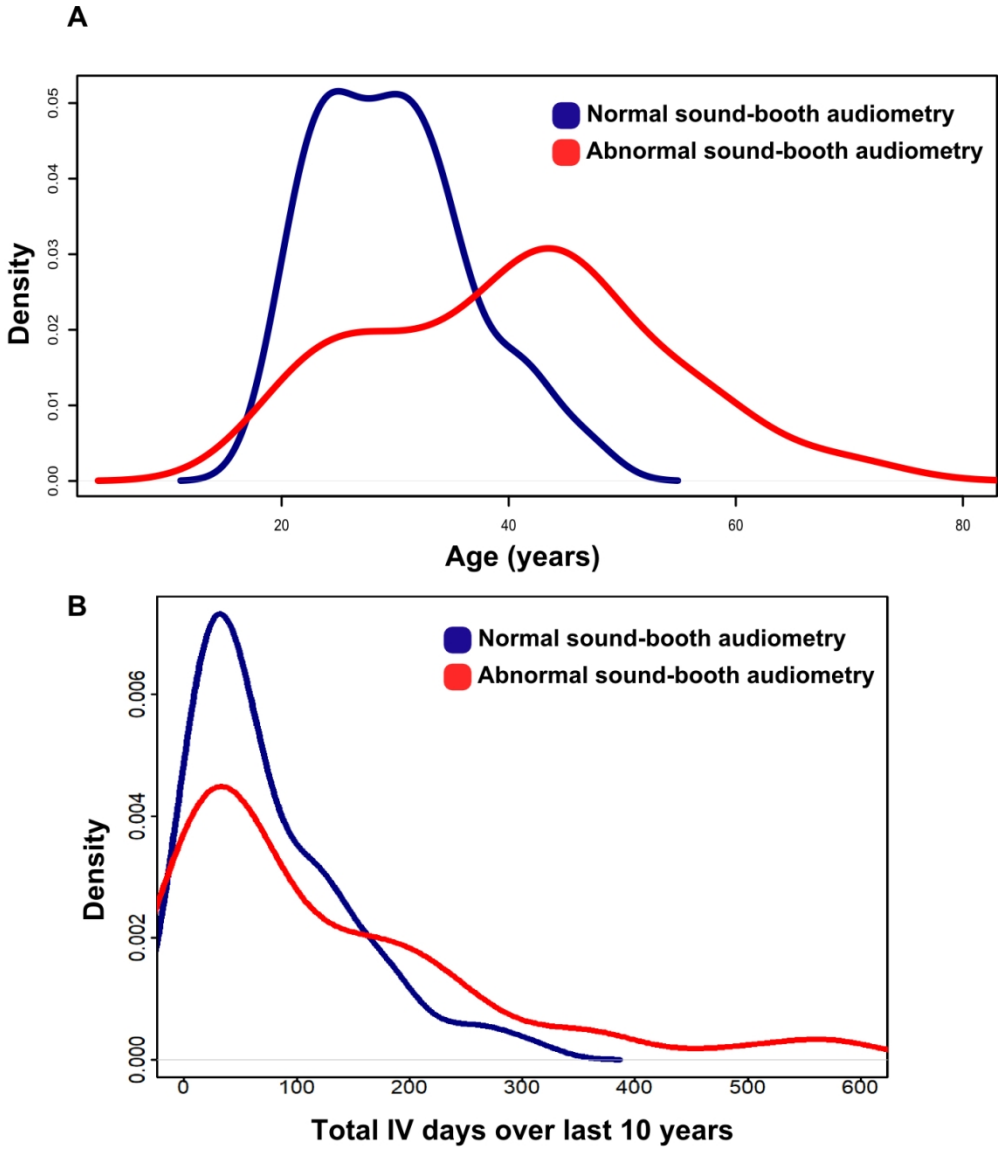


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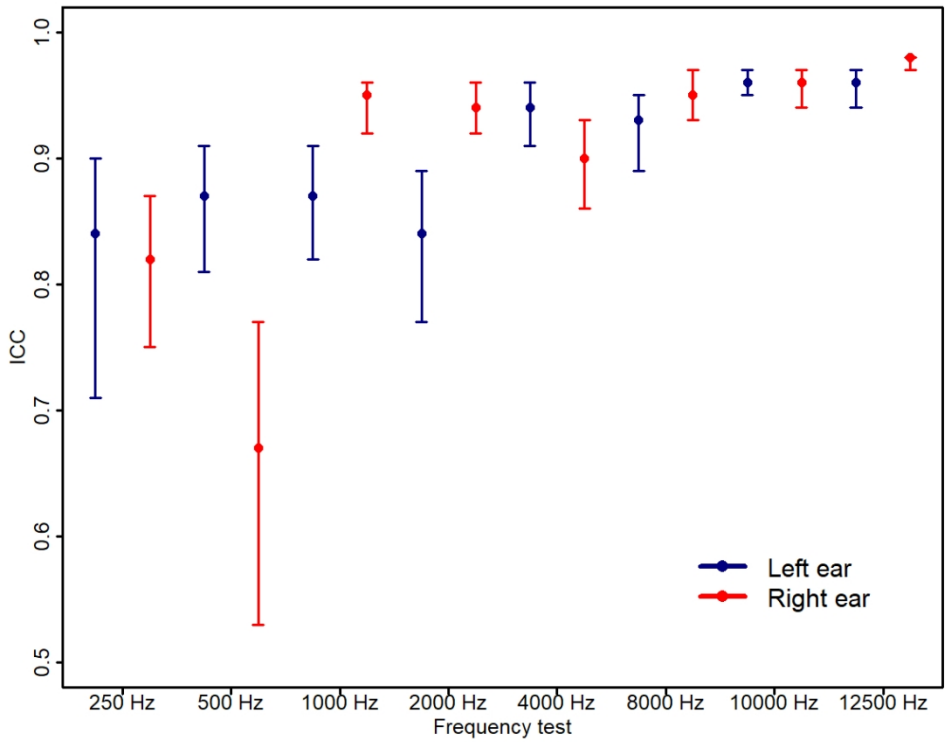


Figure 3: Intraclass correlation (ICC) analysis between tablet and sound-booth audiometry

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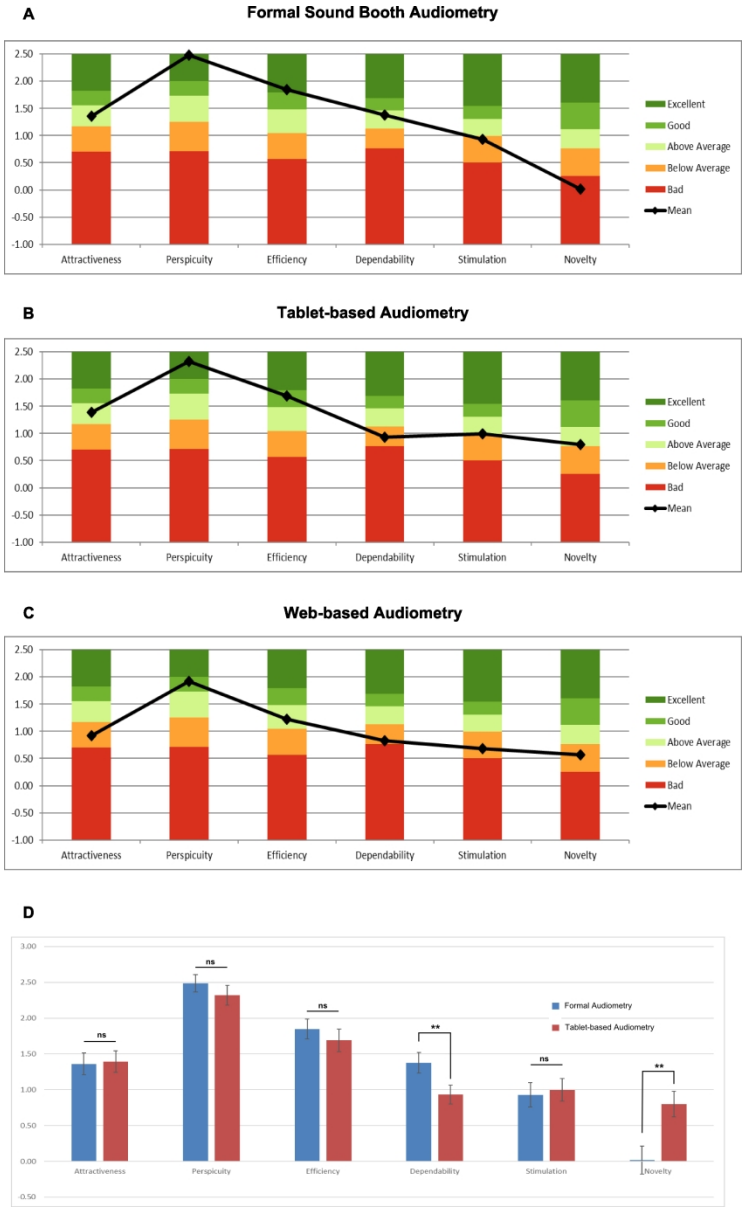


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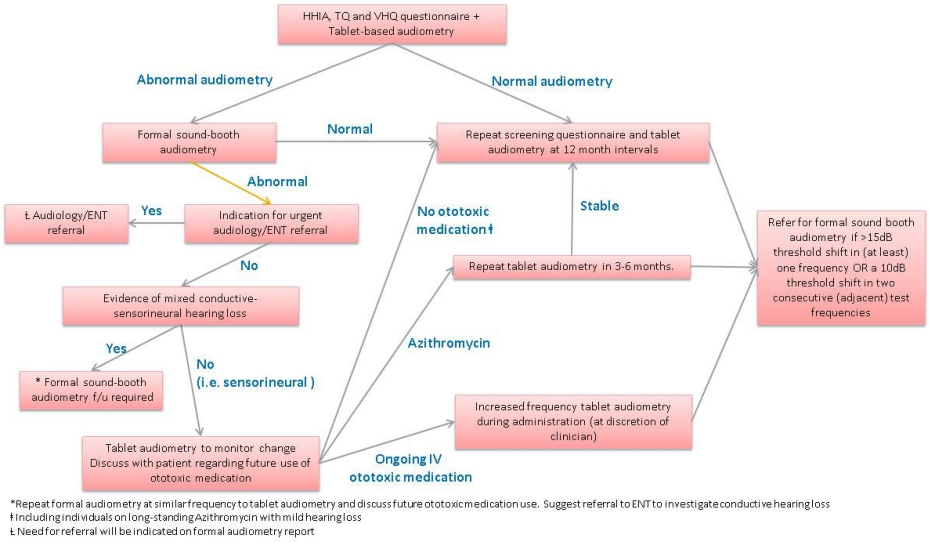


Figure 5: Proposed algorithm for an ototoxicity monitoring programme incorporating tablet-based audiometry integrated within clinical care in adults with CF.

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Supplementary data:

Study design and participants: Sample size calculation to measure reliability of tablet and web-based audiometry using intraclass correlation with a 95% confidence interval indicated a minimum of 57 patients with hearing loss would be required. Using an estimated prevalence of hearing loss of 40% and an expected drop-out rate of 15%, study recruitment target was 170. Following interim analysis as the primary endpoint was met, recruitment was stopped at 156 participants with 126 participants completing audiology test follow-up. Blood samples for mitochrondrial SNP analysis was collected from 124 participants.

Study recruitment was not targeted to those with pre-existing risk factors. The only exclusion was current use of 'hearing aids' which may have reduced overall prevalence of hearing loss in our cohort. 11 study subject had audiometric testing (web, tablet and formal audiometry) performed during administration of intravenous antibiotics.

Demographic data collection:
Total days of intravenous antibiotic use over previous 10 year period was collected through a manual data query from the United Kingdom Cystic Fibrosis registry. This would include the administration of **any** intravenous antibiotic (regardless of number of doses) at hospital and/or at home given for an infective exacerbation of cystic fibrosis (e.g. aminoglycoside, cephalosporin etc) in a single day. Chronic macrolide prophylactic use was also collected through registry analysis but was an independent variable. Given the purpose of the study was to examine the use of easily accessible data for screening stratification purpose, retrospective hand-written prescription charts were not analysed or examined.

Specific antibiotic prescription data was available and collected through electronic health record data searches from the Royal Brompton hospital for the preceding 5 year period. Data was collected for intravenous aminoglycoside and amikacin. During this period only once daily aminoglycoside dosing was used with a combination of once or twice daily amikacin dosing. During this period data was also collected for retrospective inhaled tobramycin and amikacin dosing. No other inhaled antibiotic dosing was analysed.

Mitochondrial SNP analysis: The primers, which were used for both PCR and sequencing were as follows: RNR1-aF ACTTTTAACAGTCACCCCCCA, RNR1-aR TGAGGTTGATCGGGGTTTAT, RNR1-bF ACAATAGCTAAGACCCAAACTGG and RNR1-bR TATCTATTGCGCCAGGTTTC; and resulted in two fragments of 819 bp and 729 bp spanning from m.470 to m.1727. The variant allele frequency (% in each cohort) of the 42 mtDNA variants identified in the 124 CF patients, was calculated in the total study cohort and in the cohort classified with 'normal' or 'abnormal' hearing based on formal sound-booth audiometry. Variants with rs numbers had been previously reported in dbSNP (https://www.ncbi.nlm.nih.gov/snp/). Pathogenicity classification was derived from Clinvar, MitoMap and MitoTIP (in silico prediction of pathogenicity of novel tRNA variants).

Audiometry: For all pure-tone audiometry performed regardless of device, the tones were presented for 1–2 s, with varying intervals between tone presentations. The test level of each succeeding presentation was determined by the preceding response. After each failure to respond to a tone, the

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level was increased in 5dB steps until a response occurred. After this response, tone intensity was decreased 10 dB, and another ascending series begun. Thresholds were defined as the lowest dB HL at which responses occurred in at least one-half of a series of ascending trials. The minimum number of responses needed to determine thresholds of hearing was two responses out of three presentations at a single level. A threshold of greater than 25dB hearing loss at one or more audiometric frequencies was considered to be outside the normal hearing range as per current National Guidelines for Classification of Hearing Loss.

Health economic modelling:

Given the clear increase in hearing loss seen above the age of 40, we performed a Monte Carlo simulation to compare the cost-efficiency between universal screening with formal sound-booth or tablet audiometry or limiting tablet screening to adults <40 years old given the increased probability of hearing loss above that age. With tablet screening, in the first scenario, all CF adults will be screened with tablet audiometry and those with abnormal tests will have a confirmatory formal sound-booth audiometry test afterwards. The second scenario assumes that all CF adults ≥40 years old will proceed straight to formal sound-booth audiometry testing with those <40 years old following the first scenario. The simulation was conducted in R 3.6.0. The package fitdistrplus was used to obtain the parameters for the distribution of age and total exacerbations. The age distribution was calculated from all adults with CF at the Royal Brompton and Harefield NHS Foundation Trust (539 adults). The distribution of the sensitivity and specificity of the iPad test were generated using beta distributions. The parameters for these distributions were calculated using the package epiR based on the estimated mean and confidence intervals from the analysis. We simulated the true status of 539 patients based on the multivariate model presented in the methods. The true prevalence was obtained from the simulated individual true status and the apparent prevalence (AP) was generated with the formula:

$$AP = Se*TP + (1-Sp)*(1-TP)$$

Finally, we included the cost of each test. We approximated a £2000 cost per year for the software license to conduct all iPad tests. The current NHS tarrif cost for formal sound-booth audiometric testing per adult is ~£150. 10,000 iterations of the algorithm were run.

Usability questionnaires: The UEQ was used to model people experience with each version of the test. UEQ is composed of 26 pairwise comparisons, where each item is presented as a 7-point Likert. The answers are scaled from -3 (fully agree with the negative term) to +3 (fully agree with the positive item) and measures 6 main factors: i) Attractiveness, intended as the overall impression of the product; ii) Perspicuity intended as an ability to get familiar with the product i.e., learnability); iii) Efficiency, intended as the ability of users to solve their tasks without unnecessary effort; iv) Dependability, intended as ability of users to feel in control of the interaction; v) Stimulation, intended as the ability of the product to excite and motivate end-users to use; vi) Novelty intended as the perceived level of innovation of the product. The UEQ manual offers a toolkit for the interpretation of the results and enables benchmarking of the outcomes of a new product against a validation sample developed on 246 product evaluations with the UEQ with a total of 9905 participants.

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The UMUX was applied to assess the satisfaction of use i.e., perceived usability. This short scale is composed of four items on a Likert scale from 1 strongly disagree to 7 strongly agree. UMUX offers one single metric to capture perceived usability on a scale from 0 to 100 which were regressed to a standard with a regression formula. [28,29] The benchmarked results of the regressed scores of UMUX were used to model the perceived usability of each product using the following grading scales proposed by Sauro and Lewis.[30]

Finally, the NPS was applied to evaluate the likelihood to promote the use of each product. In tune with previous research [31-33], the intention to promote is a key element to evaluate innovation and new products or services. The NPS presents a result from -100 (all end-users are detractors) to +100 (all end-users are promoters). This one item tool 10 *(Extremely likely)* to 0 *(Not at all likely)* is usually adopted in usability studies to model the likelihood of adoption of a product after its release. Results of NPS can be benchmarked against scores obtained about other products from different domains.[34,35]

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Supplementary Table 1

Average threshold 0.5-4kHz	Sex	Age	FEV1 % pred	eGFR ml/min	BMI	Recent microbiology	Mycobacterial disease (abscessus treated)	Chronic rhinosinusitis	Total IV antibiotic days in last 10 years	IV Tobramycin	IV amikacin	Inhaled Amikacin	Inhaled Tobramycin	Azithromycin
32.5	F	62	59	46	40.5	MRSA, pseudomonas aureginosa	N	N	38	3	0	0	0	N
26.9	M	57	35	90	22.0	Pseudomonas aureginosa	Y	N	222	0	15	168	596	Y
31.9	M	34	23	>90	18.9	Burkholderia multivorans	N	N	208	211	0	0	534	Y
27.5	M	30	33	>90	15.9	Pseudomonas aureginosa	N	Y	566	523	0	0	2222	Y
26.9	M	57	62	71	27.5	Staphylococcus aureus	N	N	56	0	0	0	224	Y
30.6	M	37	32	>90	20.8	Pseudomonas aureginosa	N	Y	164	0	0	0	0	Y
28.1	M	69	31	>90	23.5	Pseudomonas aeruginosa	N	N	182	172	0	0	168	N
28.1	M	21	68	>90	26.3	Pseudomonas aureginosa	N	Y	49	18	0	0	0	N
26.9	F	45	90	27	24.0	Nil	N	Y	0	0	0	0	0	Y
35.6	F	72	122	61	28.5	Pseudomonas aureginosa	N	Y	0	0	0	0	0	Y

FEV1 – Forced Expiratory volume in 1 second; eGFR – estimated glomerular filtration rate; IV – intravenous; BMI – Body mass index

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Supplementary Table 2

Mitochondrial variants	Pathogenicity classification (ClinVar/MitoMap)	Frequency (%)			Univariate analysis P-value
		All	Normal Hearing	Abnormal Hearing	
m.477T>C rs41442247	not in ClinVar/ no classification in MitoMap	2.42	2.99	1.75	1.000
m.489T>C rs28625645	not in ClinVar/ no classification in MitoMap	8.87	14.93	1.75	*0.011*
m.497C>T rs28660704	not in ClinVar/ no classification in MitoMap	4.03	4.48	3.51	1.000
m.499G>A rs3901846	not in ClinVar/ reported (Endometriosis)	2.42	2.99	1.75	1.000
m.508A>G rs113683159	not in ClinVar/ no classification in MitoMap	0.81	0.00	1.75	0.460
m.512A>C (No rs no. but reported in MitoMap)	not in ClinVar/ no classification in MitoMap	0.81	0.00	1.75	0.460
m.514_524delAC rs78907894	not in ClinVar/ no classification in MitoMap	9.68	7.46	12.28	0.382
m.514_523dupCA (No rs no. but reported in MitoMap)	not in ClinVar/ no classification in MitoMap	0.81	0.00	1.75	0.460
m.514_523dupCACA (No rs no. and not reported in MitoMap)	not in ClinVar/ no classification in MitoMap	1.61	1.49	1.75	1.000
m.517A>T (No rs no. but reported in MitoMap)	not in ClinVar/ no classification in MitoMap	0.81	1.49	0.00	1.000
m.520C>T (No rs no. but reported in MitoMap)	not in ClinVar/ no classification in MitoMap	0.81	0.00	1.75	0.460
m.568_573dupC/CC/CCC/... rs1556422469	not in ClinVar/ dupCCC: reported (Absence of Endometriosis)	4.03	1.49	7.02	0.179
m.629T>C rs201031012	not in ClinVar/ MitoTIP: likely-benign	0.81	1.49	0.00	1.000
m.669T>C rs879005843	not in ClinVar/ reported (Deafness)	1.61	0.00	3.51	0.209
m.709G>A rs2853517	not in ClinVar/ no classification in MitoMap	8.87	10.45	7.02	0.546
m.710T>C rs28358568	not in ClinVar/ no classification in MitoMap	0.81	0.00	1.75	0.460
m.721T>C rs1556422479	not in ClinVar/ reported (possibly LVNC-associated)	0.81	1.49	0.00	1.000
m.723A>C rs386828878	not in ClinVar/ no classification in MitoMap	0.81	1.49	0.00	1.000
m.723A>G rs386828878	not in ClinVar/ no classification in MitoMap	0.81	0.00	1.75	0.460
m.750A>G rs2853518	not provided/ no classification in MitoMap	98.39	98.51	98.25	1.000
m.769G>A rs2853519	not in ClinVar/ no classification in MitoMap	0.81	0.00	1.75	0.460
m.794T>A	not in ClinVar/ no classification in MitoMap	0.81	1.49	0.00	1.000

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rs1569483796					
m.825T>A rs2853520	not in ClinVar/ no classification in MitoMap	0.81	0.00	1.75	0.460
m.827A>G rs28358569	Pathogenic/ conflicting reports (deafness)	0.81	1.49	0.00	1.000
m.851A>G rs28502491 【not in ClinVar】	not in ClinVar/ no classification in MitoMap	0.81	0.00	1.75	0.460
m.930G>A rs41352944	not in ClinVar/ no classification in MitoMap	0.81	1.49	0.00	1.000
m.951G>A rs200887992	likely-benign/ no classification in MitoMap	0.81	1.49	0.00	1.000
m.956_960dupC/CC/CCC/... rs111033185 (likely benign)	likely-benign/ dupC: reported (possibly DEAF-associated)	1.61	2.99	0.00	0.499
m.961T>C rs3888511 (benign)	benign/ unclear (deafness, possibly LVNC-associated)	1.61	2.99	0.00	0.499
m.961T>G rs3888511	likely benign/ unclear (possibly deaf-associated)	0.81	0.00	1.75	0.460
m.1018G>A rs2856982	benign/ no classification in MitoMap	0.81	0.00	1.75	0.460
m.1187T>C rs111033320 (UVS)	uncertain significance/ no classification in MitoMap	0.81	1.49	0.00	1.000
m.1189T>C rs28358571	benign/ no classification in MitoMap	4.03	4.48	3.51	1.000
m.1193T>C rs111033321	likely benign/ no classification in MitoMap	0.81	1.49	0.00	1.000
m.1243T>C rs28358572	benign/ no classification in MitoMap	3.23	4.48	1.75	0.624
m.1290C>T rs1556422517	likely benign/ no classification in MitoMap	0.81	1.49	0.00	1.000
m.1406T>C rs111033322	benign/ no classification in MitoMap	0.81	1.49	0.00	1.000
m.1438A>G rs2001030	benign/ no classification in MitoMap	95.97	97.01	94.74	0.660
m.1462G>A rs111033326	benign/ no classification in MitoMap	0.81	1.49	0.00	1.000
m.1692A>T (No rs no. but reported in MitoMap)	not in ClinVar/ no classification in MitoMap	0.81	1.49	0.00	1.000
m.1719G>A rs3928305	not in ClinVar/ no classification in MitoMap	8.06	2.99	14.04	*0.043*
m.1721C>T rs200626438	not in ClinVar/ no classification in MitoMap	3.23	1.49	5.26	0.333

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Supplementary Table 3 - Usability analysis of sound-booth, tablet and web based audiometry

Scales	**Formal Audiometry**	**Tablet audiometry**	**Web-based audiometry**
UMUX and grade	77.5 (B+)	78 (B+)	72(C+)
NPS	+62	+68	+11
UEQ	**Figure 4A**	**Figure 4B**	**Figure 4C**
Attractiveness	Above Average (1.36)	Above Average (1.39)	Below average (0.92)
Perspicuity	Excellent (2.49)	Excellent (2.32)	Excellent (1.92)
Efficiency	Excellent (1.85)	Good (1.69)	Above Average (1.23)
Dependability	Above Average (1.38)	Below average (0.93)	Below average (0.82)
Stimulation	Below Average (0.93)	Above Average (1.00)	Below average (0.68)
Novelty	Bad (0.02)	Above Average (0.80)	Below average (0.57)

Supplementary Figure Legends:

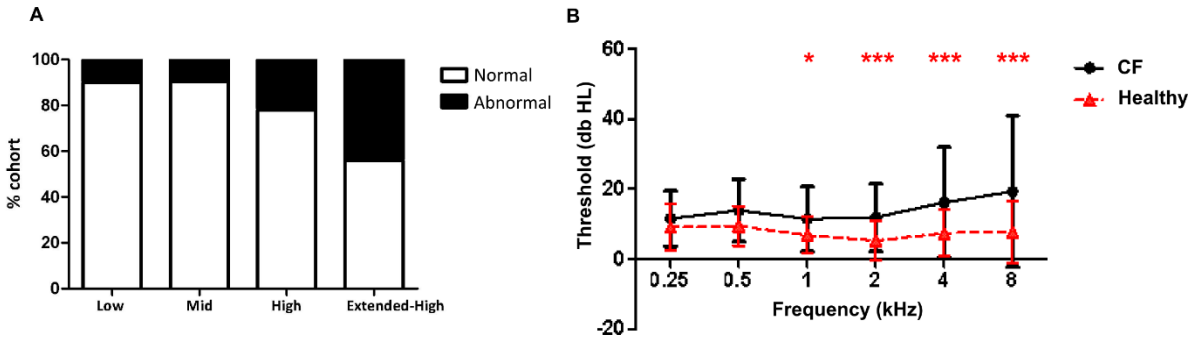
Supplementary Figure 1: A) A breakdown of hearing loss detected through sound-booth audiometry is shown by Frequency range: Low (0.25 and 0.5kHz); Mid (1 and 2kHz); High (4 and 8kHz) and Extended-High Frequency (10 and 12,5kHz). **B)** Hearing (average threshold per frequency (0.25-8kHz) in sound-booth audiometry) in our 20-29 study population (n=38) is compared to a large published cohort study of healthy 20-29 year olds (n=92). Significant increase in average thresholds is seen in our CF cohort. (* - $p<0.05$; *** - $p<0.001$)

Supplementary Figure 2: Representative Bland Altmann plots seen at **A)** low (1kHz), **B)** high (8kHz) and **C)** extended high frequency (12.5kHz) comparing tablet audiometry to formal sound booth audiometry.

Supplementary Figure 3: Audiogram showing significant aminoglycoside related ototoxicity detected by tablet-based audiometry in individual with CF. Red line shows audiogram post intravenous aminoglycosides.

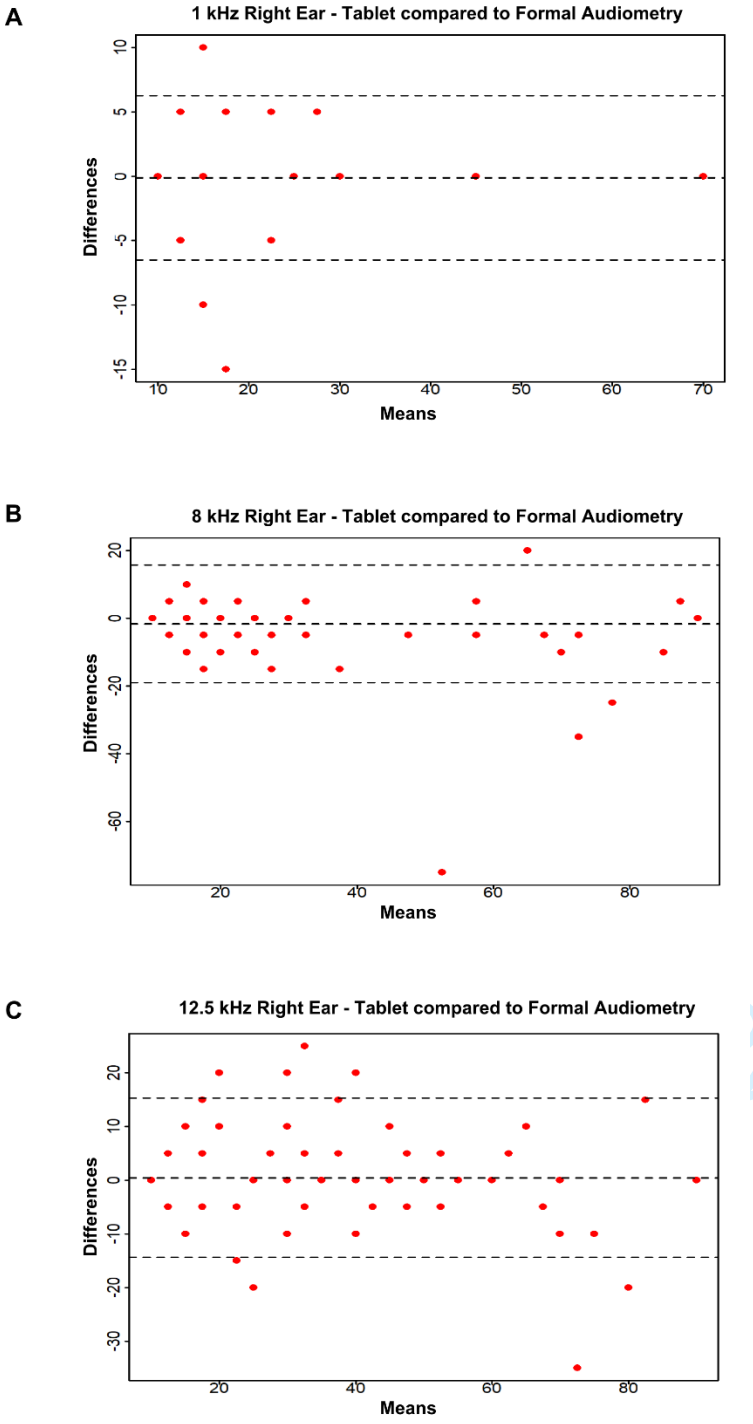
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Supplementary Figure 1



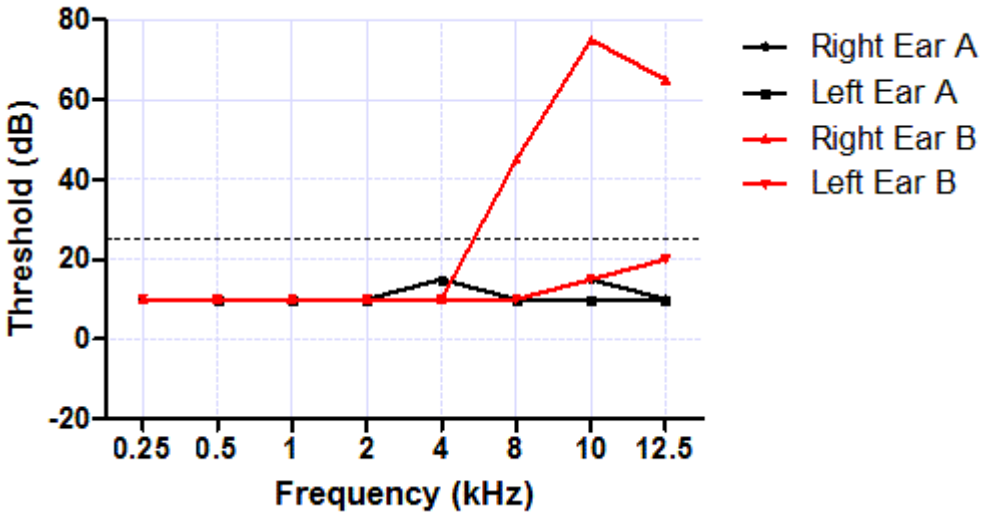
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Supplementary Figure 2



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Supplementary Figure 3



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