Bringing Innovation to Ear Infection Diagnostics

Design History File - Semester II

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Problem Definition and Need

Problem Definition

Acute otitis media (AOM), or ear infection, is the most common childhood infection. Ear infections account for 60% of antibiotic prescriptions in children, making it the main reason for the use of antibiotics in children [1]. About 60% of cases of AOM are caused by bacteria, 40% are viral or a combination of both [2]. Only bacterial AOM requires antibiotics. The use of an otoscope is the primary but inaccurate method for the diagnosis of bacterial AOM. It is estimated that 50% of antibiotic prescriptions for ear infections are unnecessary and potentially lead to a weaker immune system, expose the child to subsequent episodes of AOM, and further increase the likelihood of antibiotic resistance [3,4]. Based on a survey that asked pediatricians whether or not they would prescribe antibiotics based on different patient profiles, 45% of pediatricians prophylactically administer antibiotics, despite no evidence of bacterial ear infection.

The proper use of antibiotics shortens the duration of symptoms and reduces the likelihood of persistent infection, especially in children younger than two years [5]. Misdiagnosis and a prolonged treatment time cause the child to experience the buildup of ear pain and discomfort and increases the likelihood of hearing loss.

Need Statement

A rapid, painless, and effective method to detect whether an ear infection is caused by bacteria

Design Research

Background

Otitis media (OM) is an infection of the middle ear that can be bacterial, viral, or a combination of both. When the Eustachian tubes that connect the middle ear cavity to the nasopharynx become inflamed, they can create a blockage of middle ear fluid that can then be a breeding ground for bacteria or viruses [6]. Symptoms include mild to severe ear pain, fluid formed inside the ear, fever, loss of appetite, and trouble sleeping [6]. Otitis media is more common in young children because their Eustachian tubes are smaller and horizontal, making it harder to drain fluid [6]. About 62% of children in developed countries will have their first episode of OM by the age of one, more than 80% by their third birthday, and nearly ⅝ children will have an episode by the age of five [7]. OM accounts for 25 million doctor's office visits annually in the U.S. and costs an estimated three billion dollars [7].

Current standard diagnostic methods involve a pediatrician using a pneumatic otoscope to view the eardrum to look for redness or swelling. Another diagnosis method, called tympanometry, involves blowing a puff of air into the eardrum to observe its vibration. If the eardrum does not vibrate then there is a buildup of fluid behind it [8]. These methods provide no quantitative data on the type of infection and rely on the doctor's personal experience and judgment in assessing the problem. One diagnosis method that does provide quantitative results is called tympanocentesis. However, tympanocentesis is a last resort method used when antibiotics fail

because it involves an invasive procedure. Tympanocentesis uses a specialized needle with a tube at the end to puncture the eardrum and drain middle ear fluid for culture testing [9]. Because there is no non-invasive method for diagnosing bacterial versus viral OM, most pediatricians will work under the assumption that the infection is bacterial and prescribe antibiotics after a wait-and-see period of 48-72 hours [6]. If symptoms persist after this period of time, the doctor will normally prescribe antibiotics. This has generated concerns about antibacterial resistance caused by the overprescription of unnecessary antibiotics.

Acute otitis media accounts for 60% of the antibiotic prescriptions written for children [1, 10]. This high rate in antibiotic prescriptions is due to the lack of non-invasive bacterial AOM diagnosis methods, and because the risk of not treating a possible bacterial ear infection is too high. If the bacteria grow out of control, the patient could have permanent damage to the eardrum or mastoid bones [6]. Additionally, parents have to deal with their child being in pain and discomfort for the duration of the wait-and-see period. There is a need for a diagnostic method that gives quantitative results on whether an ear infection is bacterial or not and can also find results quickly enough to be integrated into the current cycle of care before the wait-and-see period.

Disease State Fundamentals

Anatomy and Physiology

The anatomy and physiology of the human ear is important to understand before establishing the pathophysiology for ear infections, or acute otitis media (AOM). The outer ear is connected to the middle ear by the external auditory canal or tube (Figure 1) [9]. The tympanic membrane (i.e. the eardrum) divides the external ear from the middle ear and transmits sounds from the environment to the ossicles [9]. There are three ossicles (malleus, incus, and stapes) that make up the middle ear. They transmit vibrations to the inner ear through amplification by lever action [9]. The Eustachian tube connects the middle ear with the back of the nose, which helps equalize the pressure in the middle ear for proper transfer of sound and for the proper draining of mucus or fluid [9]. The inner ear consists of the cochlea (contains nerves for hearing), the vestibule (involved in balance by responding to changes in the position of the head with respect to gravity), and semicircular canals (involved in balance by responding to rotational movements) [9]. Adenoids are two small pads of tissues in the back of the nose that are believed to play a role in the immune system and can affect the ear [8].

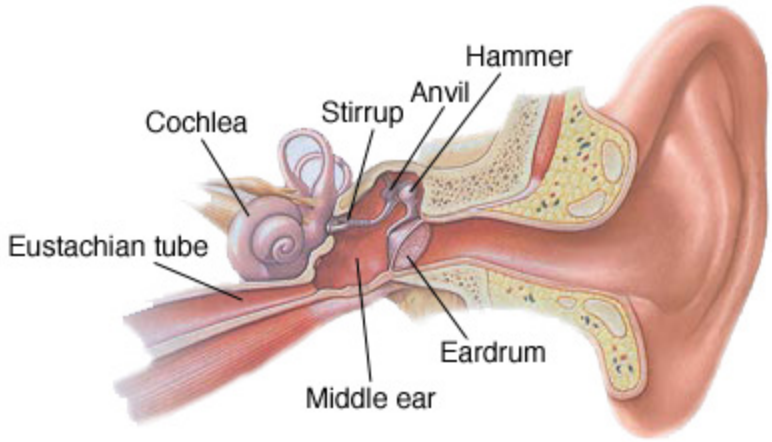


Figure 1. Diagram of the basic components of the ear [9]

Pathophysiology

The middle ear and the eardrum are the main focus of research because they are directly affected during an ear infection. There are open connections between the nose, ear, and throat that allow for the exchange of fluids [11]. The shape of the passageways between the nose, ear, and throat affect the accumulation of fluid in the ear. In children, the passage between the middle ear and the back of throat is smaller and more horizontal. In adults, this passageway has a more vertical or diagonal form allowing for better drainage of fluids or less accumulation of fluids [11]. A cold, the flu, or an allergy that causes congestion and swelling of the nasal passage, throat, and Eustachian tubes is usually the cause of ear infections [8]. Inflammation occurs in either the air-filled space behind the ear or in the outer ear canal [8]. Fluid accumulates in the middle ear when the Eustachian tubes are inflamed or swollen. Inflammation of adenoids may block the opening of the Eustachian tubes, thus leading to fluid accumulation and an ear infection (Figure 2) [8].

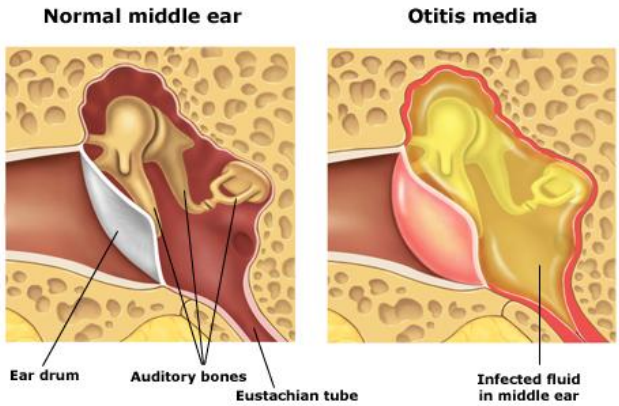


Figure 2. Diagram comparing a normal middle ear and one affected by otitis media [12]

For acute otitis media, the three most common bacterial pathogens responsible for the infection are *S. pneumoniae*, nontypeable *Haemophilus influenzae*, and *Moraxella catarrhalis* [13]. Of the three bacterial pathogens, *S. pneumoniae* was the most frequently cultured; that is, before the routine use of PCV7, a pneumococcal conjugate vaccine, started in 2000 [14]. Since then, the ordinal frequency of these three major middle ear pathogens has evolved. In the first few years after the introduction of PCV7, *H influenzae* became the most frequently isolated middle ear pathogen, replacing *S. pneumoniae*. Shortly thereafter, a shift to non-PCV7 serotypes of *S. pneumoniae* were described in the American Academy of Pediatrics guidelines. In a report that reviewed 212 AOM cases between 2003-2006, it was reported that 44% of the cases were caused by *H influenzae*, and 28% were caused by *S. pneumoniae*, with a high proportion being highly resistant *S. pneumoniae*. In that same study, 77% of the cases indicated recurrent disease or initial treatment failure. An updated report with data from 2007-2009, six to eight years after the introduction of PCV7 in the United States, showed that PCV7 strains of *S. pneumoniae* virtually disappeared from the middle ear fluid of children with AOM who had been vaccinated. However, the frequency of isolation of non-PCV7 serotypes of *S. pneumoniae* from the middle ear fluid has increased. The isolation of *S. pneumoniae* and *H. influenzae* of children with AOM has nearly equaled [14].

Clinical Presentation

The main signs of an ear infection in children include ear pain, tugging at the ear, difficulty sleeping, increased crying, increased irritability, difficulty hearing, loss of balance, high fever, loss of appetite, headaches, and drainage of fluid from the ear [8]. While these are the overall symptoms of an ear infection, they are not necessarily indicative of a bacterial ear infection. For bacterial ear infections, signs of redness and bulging in the tympanic membrane (eardrum) and the presence of pus are indicative of bacterial presence. Meanwhile, for viral ear infections, the symptoms are more systematic and not localized. In adults, the symptoms for an ear infection also include ear pain, drainage of fluid from the ear, and difficulty hearing [8].

Clinical Outcome

In some instances, ear infections will resolve on their own without the need of antibiotics, typically this occurs during a span of two weeks [8]. To lessen ear pain, patients are recommended to use methods involving warm compression and pain medication. In accordance with the American Association of Pediatrics, children younger than six months of age are immediately treated with antibiotics to resolve an ear infection [8]. In cases of recurrent otitis media, treatments includes a procedure known as myringotomy. Myringotomy provides a continual drainage of the fluid from the middle ear by creating a tiny hole in the eardrum and then inserting a tube for better drainage (Figure 3) [8]. Recurrent otitis media can result in cholesteatoma (i.e. tissue growth behind the eardrum), which can severely impair hearing [8].

Figure 3. Diagram showing the incision and tube insert for a myringotomy [15]

Epidemiology

The prevalence of ear infections is evident in children, where five out of six children will have developed acute otitis media by the age of three. The occurrences of ear infections start at an early age, where about 62% of children in developed countries will have an ear infection by the age of one [7, 16]. Nearly 100% of children will have had an ear infection by the age of five [16]. Annually, ear infections account for 25 million office visits in the United States and they are the most common reason parents and guardians bring their children to a doctor [7, 16]. Recurrence is also an issue with 40% of children having four or more episodes of ear infections. Acute otitis media is the most commonly treated bacterial infection in children [17].

Acute otitis media accounts for 60% of the antibiotics prescribed to children [1, 10]. In numerous studies, only approximately 1/3 of children initially observed received a rescue antibiotic for persistent or worsening AOM [16], suggesting that antibiotic use could potentially be reduced by 65% in eligible children. Given the high incidence of AOM, this reduction could help substantially in curtailing antibiotic-related adverse events [14]. Antibiotic therapy significantly increased the absolute rates of diarrhea between 10-20% and it increased the rates of diaper rash or dermatitis between 6-16% [14]. The overprescription of antibiotics is a major consequence associated with misdiagnosis of bacterial ear infections. Signs of antibiotic resistance are present up to 12 months after antibiotic treatment [18]. In 30% of severe *S. pneumoniae* cases, the bacteria are fully resistant to one or more clinically relevant antibiotics [19]. Resistant infections complicate treatment and can result in almost 1,200,000 illnesses and 7,000 deaths per year. Cases of resistant *pneumococcal pneumonia* result in about 32,000 additional doctor visits and about 19,000 additional hospitalizations each year [20].

Treatment Overview and Deficits in Care

Most often a patient is diagnosed using a pneumatic otoscope (Figure 4). Pneumatic otoscopy allows doctors to determine the mobility of a patient's tympanic membrane in response to pressure changes. A normal tympanic membrane moves in response to pressure while immobility due to fluid accumulation in the middle ear is an indication of an infection or other ear

problem. The pneumatic otoscope sends a puff of air into the ear and enables the doctor to observe as the air vibrates the eardrum. If fluid has built up in the middle ear there will be little to no vibration [8]. This method provides little explanation of the cause of the infection as either a viral or bacterial infection can cause fluid accumulation and eardrum immobility. A limitation to the pneumatic otoscope is that it relies solely on the sight of the caretaker and is not very quantitative. In addition, the doctor has to manually remove earwax before using the pneumatic otoscope to gain visibility of the eardrum which can be a difficult task. Tympanometry is a method similar to the use of a pneumatic otoscope (Figure 5). It also measures the motion of the inner ear, but does so using a device that seals the inner ear and adjusts air pressure. This provides a more quantitative measurement of the infection. This technique still does not provide information on the type of infection and it also requires cleaning of the ear canal before use.

Figure 4. Image of a pneumatic otoscope being inserted in a patient's ear [21]

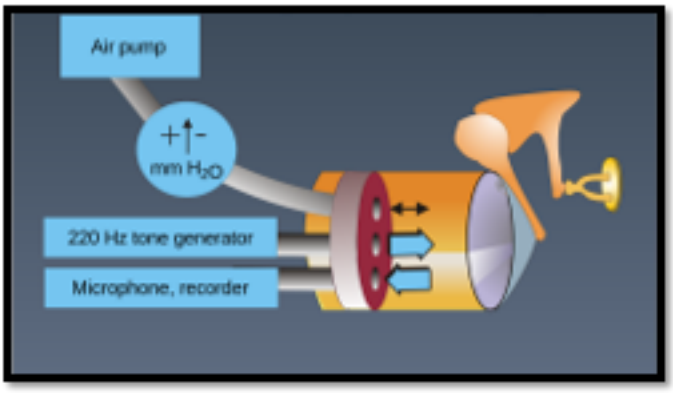


Figure 5. Schematic for tympanometry [22]

Doctors will implement a wait-and-see period for patients with a potential ear infection. Typically, this period spans between 48-72 hours after the patient has first developed symptoms. After the wait-and-see period, if the diagnosis is still not conclusive if the type of infection is bacterial or not and the symptoms are still present, doctors will prescribe antibiotics. A recent UK study showed that 55% of doctors felt pressure from patients to prescribe antibiotics even if they were

unsure of the necessity, and 44% of doctors admitted to prescribing antibiotics to get patients out of surgery [23].

For a persistent ear infection, and as a last resort, doctors will perform a tympanocentesis procedure (Figures 6 and 7). This procedure uses a tube to pierce the inner ear to drain some of the fluid and analyze it. The application of this procedure is necessary when an infection has not responded to previous treatments. This method provides the physician with information about the specific type of infection, something a pneumatic otoscope and tympanometer do not. However, this method also causes damage to the eardrum and can be difficult and unsafe for use in children [9]. In cases where the patient shows constant fluid accumulation in the ear, myringotomy is performed by making an incision in the eardrum and inserting a tube for continuous fluid drainage.

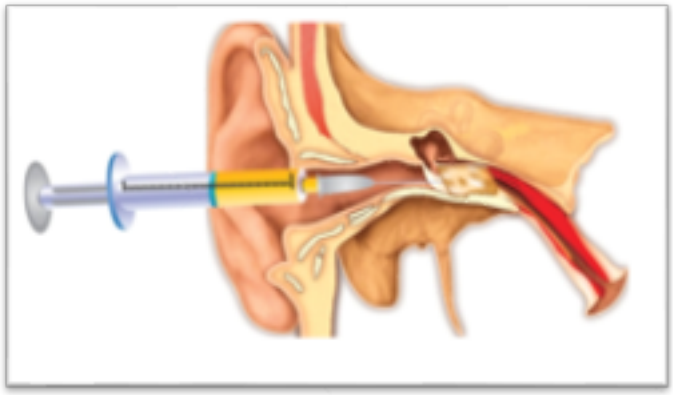


Figure 6. Diagram of a tympanocentesis procedure in a patient's ear [24]

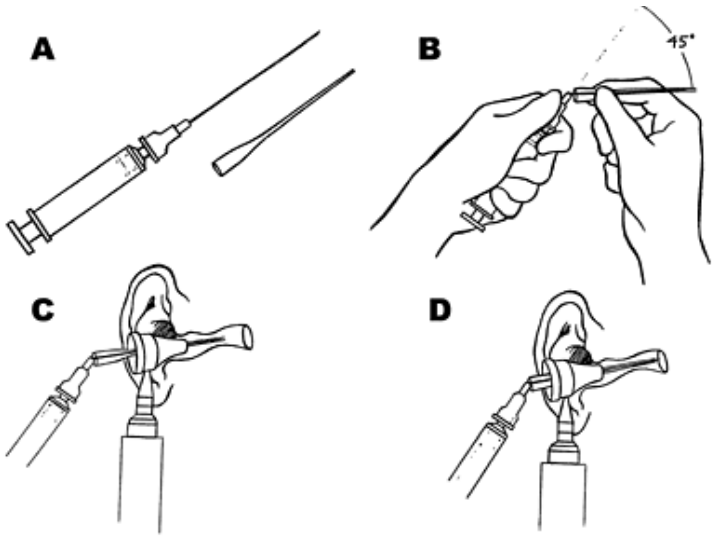


Figure 7. Diagram of the steps involved in tympanocentesis [25]

Gap Analysis

Table 1. Gaps in the current cycle of care and their descriptions

Gap	Description
Lack of accurate results	● Current non-invasive approaches provide little explanation of the cause of the ear pain and they do not provide information on the type of infection. ○ Otoscopes only provide a view of eardrum surface. ○ Tympanometry only provides data on eardrum hypermobility. ● Most of the current diagnostic methods rely on a doctor's experience and are therefore not quantitative. ● Doctors prescribe antibiotics even with little evidence of a bacterial infection, increasing the likelihood of antibiotic resistance.
Treatment time	● Tympanocentesis, followed by a culture and sensitivity test, is the only way to identify the bacteria causing an ear infection. However, this is only performed towards the end of the cycle of care when prescribed antibiotics have failed to respond. This prolongs the treatment time from several days to several weeks. ● The wait-and-see period is about 48-72 hours. But if we can determine a need for antibiotics earlier than this wait-and-see period, then this step in the cycle of care can be eliminated, thereby decreasing the total treatment time. ● It takes about 48 hours to notice whether the antibiotic treatment is working or not.
Discomfort and pain	● Children with AOM experience pain and discomfort during the wait-and-see period, something parents and guardians need to deal with. ● The tympanocentesis approach, which entails puncturing the eardrum, is invasive. Performing surgery on a child is not a desired diagnosis method.

Economics of Care

Children with ear infections have an average of two more outpatient visits, 0.2 more emergency visits, and 1.6 more prescriptions filled than children without ear infections [26]. The direct cost for ear infection treatment is estimated to be $3 billion annually [26]. Taking into consideration the opportunity cost (time and work hours), health economists estimate the total cost of ear infection treatments to actually amount to $6 billion annually [8]. Per year, $314 are spent per child on outpatient care plus $17 per child for additional costs for medications [26].

Design Input

Stakeholders

We anticipate our customers to be either pediatricians and family physicians, parents and guardians, or clinics and hospitals. The physicians or parents will most likely be the end users because they will be the ones using the diagnostic tool on the child.

Table 2. Stakeholder Chart

Customer	Role	Primary Benefit	Primary Cost	Net Impact
Physicians	Influencer	Will be able to determine whether an ear infection is bacterial	Cost of learning how to use the diagnostic tool	Positive: Physicians will know whether or not they should use antibiotics to treat the ear infection and the proper usage of antibiotics also helps lower the emergence of bacterial resistance.
Parents	Influencer	Will be able to determine whether or not their child requires antibiotics	Cost of device/ diagnostic tool, cost of possible treatment, as well as cost of learning how to use the diagnostic tool	Positive: Parents will know whether or not antibiotics are necessary, and if not, they will save money.
Clinics/ Hospitals	Decision Maker	Will be able to purchase less antibiotics due to better use of the antibiotics stock	Cost of purchasing the diagnostic tool and training medical staff who will be using it	Positive: Clinics and hospitals will make better ear infection diagnoses and save money due to better use of antibiotics.

				This will also help prevent the emergence of bacterial resistance in hospital settings.

Cycle of Care

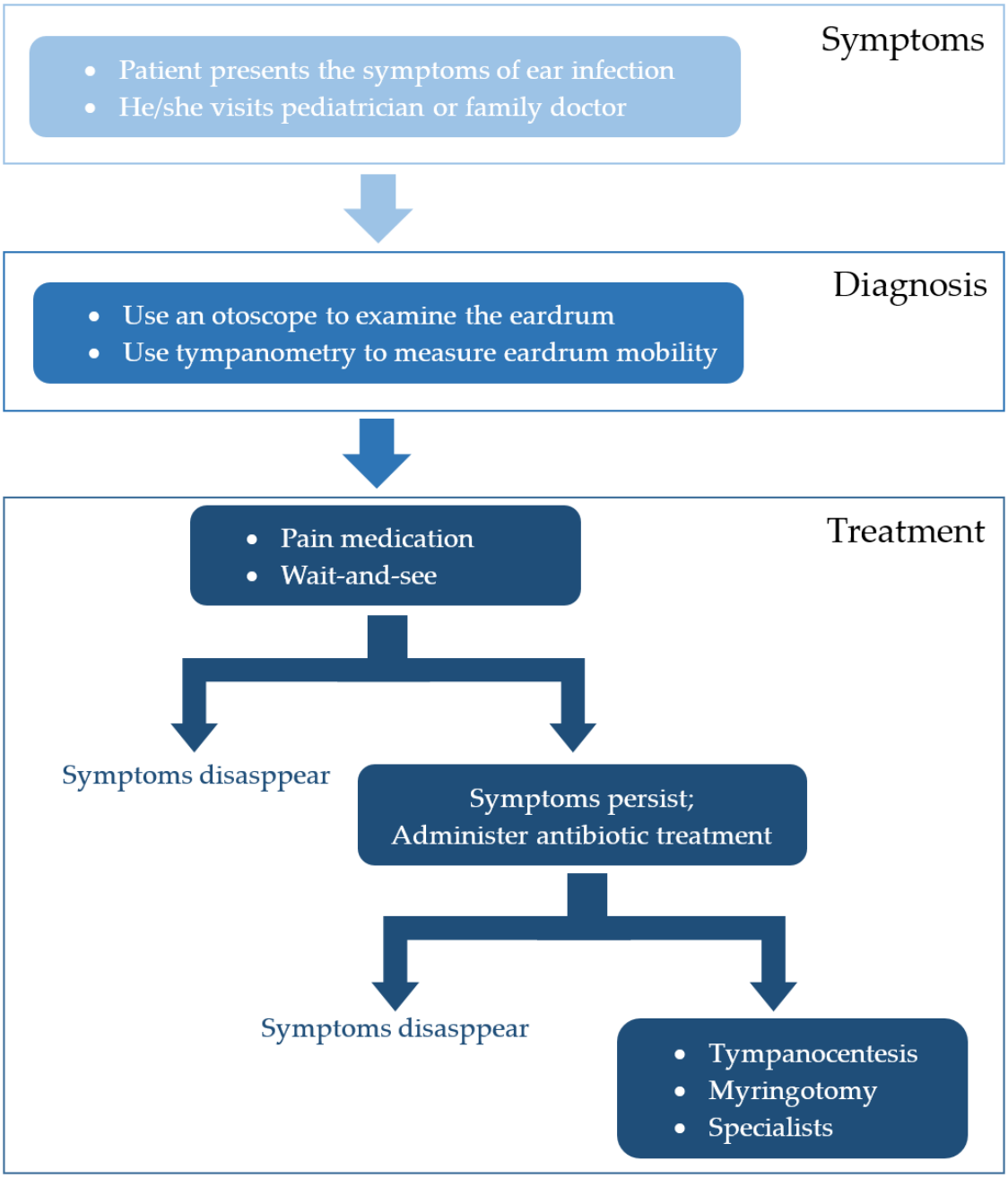


Figure 8. Flow chart for the cycle of care for ear infections in children with a gap at the diagnostic level

Our cycle of care (Figure 8) begins with the patient developing and showing symptoms. Typically, a child will first show symptoms for ear infections, such as ear pain, tugging or pulling at the ear, difficulty sleeping, loss of balance, and a fever. After the child expresses the symptoms, they are taken to the pediatrician for a checkup.

From there, there are two currently prevalent methods of diagnosis. The most common one is using a pneumatic otoscope to check for redness and bulging of the eardrum or leaking fluid. The other method is tympanometry which involves using a puff of air to measure eardrum movement. A distended eardrum is not compliant, indicating an infection. Normal tympanometry readings show a spike in the emittance graph for normal, healthy eardrum movement as opposed to a stiff eardrum which has a flat reading. This, in combination with the ear canal volume, can indicate whether there is fluid behind the eardrum or a perforation on the eardrum.

Due to the inconclusive nature of these diagnosis methods in determining if an ear infection is bacterial or not, the doctor will use the wait-and-see approach. In addition, the doctor will prescribe pain medication if the pain is greatly affecting the patient. In this part of the cycle of care, the patient is not able to get a confirmation of the cause of the symptoms, so there is a prolonged treatment period.

If the symptoms do not go away on their own, antibiotic treatment is prescribed. If the symptoms continue beyond that, the patient may enter another cycle of care with alternative diagnostic methods. Tympanocentesis is performed to remove fluid from behind the eardrum by piercing the eardrum. This restores the pressure inside the ear to reduce pain. It is usually followed by a culture and sensitivity test of the fluid sample for analysis. In most cases, the culture and sensitivity test can identify the cause of the infection and/or the bacteria that is causing the infection [16]. This diagnostic method helps the doctor prescribe an antibiotic that is more likely to work. But sometimes no bacteria is found in the fluid, indicating the cause of ear pain is OME instead of AOM. Myringotomy is performed when patients have persistent fluid presence for over three months. This procedure involves creating a hole in the eardrum for continual fluid drainage. If none of the treatments are working or if the cause of the ear pain is not apparent, the patient will then be referred to other specialists.

<u>Key Interviews</u>

1. In-Person Interview with Dr. Ana H. Kim, CUMC Director of Otologic Research:

   Q: *We want to understand what the guidelines are and how you determine whether or not to give antibiotics because we have noticed that a lot of papers usually mention antibiotic resistance and how that is becoming an issue, so we do not know if that is an actual concern.*
   A: It is and unless there is gross middle ear pathology or there is fluid or pus, it is limiting. The ear is unfortunately a bystander, so if there is something going on in the nose or the throat, the ear is going to be a bystander of that infection. If there is nothing

in the head and neck exam or absence of the pus then I tend not to prescribe antibiotics and that is the guideline. If you are not seeing physical findings of bacterial infection, you should not be giving them.

Q: *So you follow the wait-and-see approach, correct? Do you think that a better diagnostic solution might be able to make this period quicker, like knowing whether or not an antibiotic is necessary?*
A: [Ear infection diagnosis] is purely based on physical exams, but unfortunately, pediatricians use a handheld otoscope, which does not really give you a clear, in-depth perception. So, the kid is crying in the doctor's office and their eardrum is red, so the pediatrician by reflex is just going to prescribe antibiotics because it gives the mom something to go home with. Maybe this will help the pediatricians and general practitioners, not so much with the ENT where we are actually looking in the microscope and we are looking for the presence of pus. So yes, it could be applicable to the generalists, family doctors, and pediatricians, if you can distinguish between the two.

Q: *What are some safe measurements that can be taken on the ear?*
A: Well, right now what we do is pneumatic otoscopy, it is called emittance, so basically the eardrum should be nice and flat and the middle ear should be filled with air so within the external auditory canal we create a seal and get a pump of positive pressure, so if the middle ear is full of air it should move. So the emittance should be a nice sharp peak. If there is fluid behind the eardrum, you apply pressure, but it is not going to move due to the presence of the fluid. So then, you will have what we call "flat temp". It is non-invasive and does not cause any damage to the eardrum. You just insert a probe and it will just measure out the movement of the ear. Some people call it tympanogram.

Q: *Is that the main method that you use?*
A: You are talking to a very biased person, we are actually physically looking to distinguish between infected ear and not infected. Pediatricians rely on pneumatic otoscopy. Walk-in clinics do not even rely on that. They just use a normal otoscope then most likely prescribe antibiotics.

Q: *Do you think that antibiotic resistance is enough of a severe factor for a project like this?*
A: I think so, yes, even in adults. On a weekend, for example, an adult has an ear pain, they go to a walk-in clinic, they say they have an ear infection and are given antibiotics, yet a couple days later, it looks like there was never an infection. So it is also an age group issue.

Q: *How many of these infections are viral, relative to bacterial?*
A: I would say is that there is a small percentage, but what would matter is eradicating those that are neither bacterial or viral.

Q: *Based on your work, have you seen any other projects like this that can help guide us? Is the problem more in non-invasive imaging?*
A: Right now, the tools that we have are CT imaging which requires the child to be still so they have to be sedated and puncturing the ear to get the fluid. There is a delay of 48-72 hours emittance, if the probe is not fitting correctly, you will get an artificially flat reading. You would want a simple solution that spits out specific/sensitive information. Spitting out some type of statistic of probability rapidly would be better. If you can manipulate the eardrum with ultrasound or something to gauge a change in the air pressure or volume, then we would have a sensitive way to see if there is inflammation, fluid, or pus. It would be great to assess the ear using a probe that could be gently placed to minimize any pain.

Q: *So these changes only happen for ear infections?*
A: The eardrum is very thin, although it is three layers, but during the ear infection, the layers thicken so it will be helpful to get the status of the eardrum and the status of the middle ear. So, to emphasize, you should focus on the TM thickness and position and status of the middle ear.

Q: *What could we create that may be related to imaging?*
A: If you can take a picture and someone how get a 3D view of the ear, you can get a better idea of whether the ear is flat or retracted and you can assess the thickness of the eardrum.

Q: *Can you explain more the change in thickness?*
[A diagram was drawn and explained]

Q: *How do you distinguish fluids seen in the ear? What if the fluid is associated with something that is not an ear infection?*
A: With congestion, there can be serous fluid, which is not necessarily associated with ear infections. Instead, the fluid needs to be opaque and pus-like.

Q: *What would be appropriate materials to model the eardrum?*
A: Something useful may be materials like cellophane and saran wrap which work really well because they are clear and flexible.

2. Phone Interview with Eli Grunstein, CUMC Professor of Otolaryngology Head & Neck Surgery:

Q: *Based on the problem statement, are there are any current solutions that specifically differentiate between the two ear infection types?*
A: There is honestly no obvious testing or culture. Pediatricians just manage ear infection procedure to their best abilities. If anything, we have seen there are more extreme symptoms with bacterial ear infections compared to viral ear infections, but

there is not really a way to quantity. If viral, a child will show less symptoms and have less pain.

Q: *What is the current diagnostic procedure that pediatricians go through now?*
A: So looking at the guidelines, according to the American Academy of Pediatrics, there are some key action statements, divided into two categories: severe versus nonsevere and unilateral versus bilateral. If a child has a severe ear pain in one ear and the child is six months and older, the child will be prescribed with antibiotics. If the child has non-severe pain in both ears and the child is 6-23 months, the child will be prescribed with antibiotics. If the child has non-severe pain in one ear and the child is 6-23 months, the pediatrician has the option to either observe and go through the wait-and-see period or prescribe antibiotics. Before the guidelines changed recently, about two years ago, children were always getting antibiotics, regardless of the age or initial ear conditions.

Q: *What are the main concerns of overprescribing antibiotics?*
A: Some of the other concerns include developing an antibiotic allergy and experiencing side effects to taking these antibiotics so often. Such side effects, also known as a secondary infection, include vomiting, rashes, and diarrhea. Another concern is the potential overgrowth of bacteria. A lot of us specialists are trying to prevent the spread of ear infections to the other parts of the body, such as intracranial infections or mastoiditis, which is why pediatricians are naturally inclined to prescribe antibiotics to avoid such an issue.

Q: *Do you think that finding a solution to this problem would be valuable overall?*
A: It would be amazing. In fact, if you find a solution to this problem, you just might win a Nobel Prize. I really think that would make a significant impact for the pediatricians who will most likely be the ones using the product.

Q: *What would be the possible downfall of any solutions that are directly testing the bacteria or viruses?*
A: It would be very expensive to do PCR and getting a culture and it will also take a couple days, whereas we would be want something that takes less time to provide results.

Q: *Are there ever circumstances when the child does not even have an ear infection and just has some other type of ear problem?*
A: Well, there are some people with ear pain that sometimes do not have an ear infection, so in that sense, there is some misdiagnosis for those in that category. However, this does not happen very frequently, so I would not focus so much on this. For example, a lot of people go to the doctor because they have “swimmer’s ear” or a fungal infection or they have an infection on the outer surface of the eardrum rather than the inside, but, once again, this is pretty rare.

3. Phone Interview with Dr. Naazneen Iqbal, Pediatrician

Q: *What is the cycle of care you follow when a patient comes in complaining of a possible ear infection? What is the process for patients who have ear infections?*
A: I have only been in practice for a year, so I follow the 2011 AAP guidelines for diagnosis and this is what doctors should be following. Typically doctors who have been in practice for more than 20 years will follow a more conservative approach and be aggressive with antibiotics. Currently there are vaccines against the common bacteria that cause ear infections. When it comes to administering antibiotics for a patient with a possible ear infection, it really depends on the age and that determines how quickly we will place the child on antibiotics. If the child is younger than six months, the use of antibiotics is guaranteed because it is difficult to enter the ear and check at that age. If the patient is between six months and two years and the symptoms include ear pain, fever, and have lasted for than 48 hours, they will also be placed on antibiotics. Typically, if there is a fever, the patient will be treated with antibiotics. Antibiotics are immediately prescribed if there is bulging of the eardrum and pus because this is an actual indication of a bacterial infection. Symptoms such as redness of the tympanic membrane are more subtle symptoms that do not necessarily indicate a bacterial infection. Age really matters in deciding the prescription of antibiotics and there always exists a concern that the patient will not respond well and can develop additional symptoms such as diarrhea.

Q: *What are the current tools that are used to make an ear infection diagnosis? What are some of the safety concerns with these tools? What do you perceive is a challenge with detecting the cause of the ear infection?*
A: *S. pneumoniae* and *influenza B* have vaccines and the infections caused by these strains have declined. The gold standard for diagnosing ear infections is the tympanogram which looks at pressure. Typically, this exam is conducted by an audiologist or an ENT. For the general pediatrician, a procedure that uses a puff of air allows for the observation of the eardrum to see if it is moving or not. A normal eardrum moves with the puff of air but an infected one does not. Not everyone is trained to do this procedure and it is actually difficult to get a proper seal in the channel. Most clinics use disposable attachments for their otoscopes and these provide less of a seal and it is difficult to not use these disposable ones without running into the problem of sterilization. It is important to perhaps develop a more user-friendly method for diagnosis.

Q: *Why are ear infections more prevalent in children than adults?*
A: The middle ear in children is more horizontal while the middle ear develops vertically or diagonally in adults. Infections develop because of the accumulation of mucous in the middle ear. The mucous acts as a medium for microorganism growth. The vertical middle ear allows for draining of fluid and in children this draining is not possible.

4. In-person Interview with Nicholas Arpaia, CUMC Assistant Professor of Microbiology & Immunology

   Q: *How do you know if something is bacterial or viral?*
   A: In general, what would be different is culturability. There are stuff specific to cell wall components. It is worth looking into the specific strains that cause ear infection. Find out if they are gram-positive or negative (a lot of bacteria that cause infections are purple on gram paper). You can also find the unique surface products. But you need to be aware of the common surface products, they are the ones that can be found on the normal uninfected skin, which will cause a problem with the assay.

   Q: *What are some safe tests? We heard about ultrasound.*
   A: Problem with DNA or RNA based test is that it takes time but you want it to be quick. Assay on some proteins is the fastest way. For example, there are detection based method with antibiotic reaction, a rapid test like the strep test. With that, you need to find something that is bug specific. Several sources to look for proteins related to bacteria or genes: NIprobe (about proteins), NCPI (genes). If you want a non-invasive method, ultrasound can be a good idea. But there is a problem of how to do it. You can also consider distinguishing heat signature or density between viral and bacterial infections.

   Q: *How prevalent is antibiotic resistance?*
   A: Antibiotic resistance is a huge problem. A lot of the times, we have a local infection, but we treat it with systemic antibiotics because we do not have a good way of topically getting that area treated. What you are concerned with is having a deep area infection spread systemically. But in the case of children with ear infections, they start complaining very soon after the pain is there and they are showing that this local treatment is sufficient in the New England Journal. With regards to treatment, there is an eardrum based antibiotic that can treat these bugs. Even when using it to treat viral infection, it is seemly better because it is not causing systemic resistance. But if you are looking into whether or not to treat, then detecting the bugs themselves is important. You can use an example of the fact that we have a strep test in the doctor's office. During strep test, the doctor swabs you and does the immediate test to decide if antibiotics would be beneficial to you. Because there is a concern that we are developing a broad spectrum resistance against these things, they do not want to give you antibiotics when you do not have something since there is a chance you might pick up something that is resistant.

   Q: *Can we apply a test like the strep A test to diagnose ear infection?*
   A: For example with STDs, there are 2 ways of detecting them. First is the indirect method, which relies on detecting the host response to a specific bug. It looks for host antibiotics against pathogens, which means it is testing your response against pathogens. The other kind is a direct test. There are multiple types and some take longer than others. The first one looks for bugs/pathogens using purified antibiotics (reagents available) against the bugs. This is rapid! The second one is nucleic acid based

amplification. You take the DNA or rDNA of the sample and amplify it with specific primers for that bacteria and they are a lot sensitive. The last one is culture based. You plate samples on different media and see if they survive or not. This takes as long as it takes for the bug to grow. The direct methods are the best bet.

Q: *Where else can we get the sample non-invasively for ear infection?*
A: With ear infection, the circulating lymph sites might have the bacteria. Maybe you can swab the back of throat or nose.

Q: *What should we ask to medical biologist?*
A: You should ask what plates they are growing the sample on and why. This relays to what the bacteria need in order to survive and what they make when they are surviving. You can also ask what bugs you usually pull out when you have ear infection versus when there is none if you culture the swab from the ear.

5. In-Person Interview with Rahmatullah W. Rahmati, Assistant Professor of Otolaryngology

Q: *What is the range of frequency appropriate for ear imaging?*
A: Hearing tests have a range around 8 kHz.

Q: *What is your opinion on ultrasound imaging of the ear?*
A: Ultrasound is interesting, but from a product development perspective, there is no utility.

Q: *What can you measure in the ear that is safe? Like heat signature?*
A: I do not know how it would be done. But in addition to ear anatomy, you need to factor in the fact that the squirming little kid is a challenge to examine. You would want to be less invasive so it is easier to collect the measurements. You also need to consider much more for ruptured eardrum.

Q: *Is it possible to apply a test like the strep A test to diagnose ear infection? Where else can we find fluid sample?*
A: If the ear is ruptured, we can get fluid. Otherwise, there is no other access to the fluid behind the eardrum. If you swab the ear, you will just get wax and the nose is full of bacteria. You do not need additional tests to distinguish the difference between bacterial and viral infection, you just need to listen to the patient because in terms of clinical practice, viral infection is systemic and bacterial infection is localized. We check for a cough, running nose, and body ache to conclude if it is a viral infection. Culturing sample can be useful for people with chronic infection that have developed drug resistance. It can be used to check the sensitivity to different antibiotics and help the doctors to determine the right one. On the other note, maybe you should distinguish OME from AOM instead, because those people can not hear well. There are two groups of kids

affected by this: 1) kids who have recurrent infections, that means six or more per year, 2) kids with persistent fluid for over three months.

Q: *How can you make the diagnosis more accurate?*
A: You can integrate clinical guidelines, PubMed findings, and physical exam measurements to render a more sensitive diagnosis. This can take it to the next level of accuracy by having thousands of otolaryngologist putting in their personal experience.

Q: *How confident are doctors with a diagnosis that is based on guidelines?*
A: I do not think we have data to show accuracy. The reality is, 85-90% time, doctors judge based on personal experience.

Q: *What are some other ways to check for an ear infection?*
A: One of the other criterias is hypermobility. A bulgy distended eardrum is not going to be compliant. One thing we have is tympanometry. Normal readings have a spike. Stiff eardrums have a flat reading. This in combination with the ear volume tells you if there is fluid or a perforation (ie. eardrum with a hole). The way to distinguish is to measure the canal volume. If the volume is huge, eardrum is ruptured. Maybe you can create a camera with tympanometer. It can give an image and audio matrix, which tells you whether there is a decrease in compliance or not, whether the eardrum is stiff or bulgy even in the presence of wax (which could obscure the normal otoscope view).

6. In-Person Interview with Ivy Schultz, Columbia Engineering Associate Director of Entrepreneurship, Mother

Q: *Can you walk us through your experience with ear infections in your child? What drove you to go to the pediatrician?*
A: There was a period when my son had about 4-5 ear infections last year, between the age of 5-12 months. He was too young to communicate, so he was not tugging his ear and was obviously not able to tell me and my husband that his ear was hurting. He was just crying a lot and had a cold and fever every time. He would eventually start to tug on his ear a day or two after the cold would start. We took him to the pediatrician the first couple of times, and they eventually prescribed antibiotics, but, to be honest, I never gave them to him.

Q: *Why did you not want to give the antibiotics to him?*
A: Well I just think they can be pretty dangerous if overused and I am not trying to introduce antibiotics so early to my child to the point that he becomes dependent on them. I am just privileged to have done a lot of research, due to being a very educated person and paranoid parent. I have actually learned about some home remedies, such as exposing my son to raw garlic, to treat him, which has avoided antibiotics completely. I am actually a part of a mother's group in the city and a lot of us feel this way. Partially

because I have educated them a lot on this over the past couple of months. I think that there is an overall lack of education on why antibiotics are dangerous.

Q: *Was he given the same prescription each time?*
A: Yes and no, our pediatrician increased the dosage the second time he got the ear infection, but started to change the prescription afterwards because she thought the antibiotics were not working.

Q: *Has this experience pushed you to learn more about how ear infections work?*
A: Yes, I have done a lot more research on pediatric ear infections and maybe if there were easier ways for me to identify them it would prevent me from going to the pediatrician, since all they are going to do is prescribe antibiotics. I would rather just know when he has it, then use my home remedies to treat it.

Q: *How long did it take for the ear infection to clear up?*
A: About a week.

Q: *Were pediatricians concerned about the frequency of the ear infections?*
A: Yes, that is the main reason why we still end up going to the pediatrician for check-ups and ask about that, just to make sure that there is not actually something wrong. Like, maybe there are concerns about hearing loss and ruptured eardrums, especially since my husband has a history with ear infections and we were suspecting that there was some type of genetic inheritance that occurred.

7. E-Mail Interview with David Gudis, CUMC Professor of Pediatric Otolaryngology

Q: *Based on your experience, do you feel like our problem statement is a prevalent issue?*
A: Yes, definitely. So I do not entirely know what the pediatrician may be going through when diagnosing ear infections, but I do know that, although most are bacterial, there are some that are viral, or neither, or both, and qualitative information is not going to tell you much about those. There needs to be a way that rules out all other possibilities of what the source of the infection may be, as means to come up with the most efficient treatment that is actually going to work. Yes, pediatricians have to adhere to guidelines, so they are not just giving antibiotics purely on previous knowledge. There have been improvements on the guidelines in the past couple of years to reduce the prescription of antibiotics.

Q: *Do you know of any current solutions in the market right now?*
A: No, the only technology that at least gives a better idea of what is going on behind the ear requires using imaging techniques and CT scanning.

Q: *If you were to compare techniques in imaging and microbial detection and others, which one would make the most sense for this problem, given the anatomy of the ear?*
A: I would say that having some type of 3D imaging technique would at least provide some more information to the pediatrician, even it does not give a concrete quantitative value.

8. Phone Interview with Aisha Nagarwala, Penn State Marketing Graduate, Mother

   Q: *What leads you as a mother to the take your child to the doctor? Does the child complain about the pain or show any symptoms?*
   A: My daughter, Seher, will usually say that her ear hurts and will constantly be pointing at it or touching it to show that she is in pain. Additionally, I notice that she is suddenly very tired and a lot more irritable. The time she had an ear infection, I did not notice any signs of a fever. It was mainly just the ear pain and that is enough for me to decide to take her to the doctor.

   Q: *After the initial visit to the doctor's office, how long does the parent have to wait before going back for a follow-up?*
   A: My daughter's doctor immediately prescribed her amoxicillin. However, the ear infection and its symptoms were not actually going away. We had to go back in a week and then my daughter was prescribed a stronger antibiotic. When my son had an ear infection, he was also prescribed amoxacyin. He had negative reactions to this medication and we had to go back the following day for him to receive a different prescription.

   Q: *Do you feel antibiotic resistance is something to be concerned about with the constant prescription of antibiotics in children?*
   A: I am fine with my children being prescribed antibiotics as long as it is not on a constant basis. I would definitely feel better knowing that the prescription of antibiotics is being done on a need-be basis and that my children are not being prescribed antibiotics when they do not need them.

   Q: *Have you noticed a high frequency of ear infections per child?*
   A: Thankfully, both Seher and Amaan have only had one ear infection each. With Amaan still being young, I do hope that he does not develop any more ear infections.

9. E-Mail Interview with Joseph Haddad, CUMC Professor and Vice Chairman of the Department of Otolaryngology

   Q: *Do you know of any upcoming research on the diagnosis of bacterial ear infections? Any papers or techniques to look at?*
   A: Google SG-AR. It's the newest method I know of for testing this sort of thing. I think it is most likely to relate to what you guys seem to be working on.

Q: *What methods do you typically use to differentiate between bacterial and viral ear infection?*
A: Most of the time I just rely on a visual, but that's probably not what you're looking for here. One difference that could be helpful is a thicker fluid is more likely to be pus which would mean bacteria. More pus typically means the membrane is more opaque as well.

Q: *Other otolaryngologists have told us accessing middle ear fluid would not be the safest way to go about this. We have been considering using an imaging based solution or big data. Do you have any thoughts on either of those?*
A: SG-AR, like I said before, is a new method you could look into imaging wise. As for big data I do not particularly know much about it.

Q: *If we are going to go with imaging, what material would you suggest we use to model the ear?*
A: The eardrum is a three part membrane made mostly of skin. Simple material like alloderm would work for what you are going for. If you do end up making a functioning model people would be interested in that by itself. It could be used for surgery and tube tests.

10. In-Person Interview with John Wright, Assistant Professor of the Department of Electrical Engineering and Data Sciences Institute

A: ...That's the main advance that we have made in scientific imaging in the past 20 years. It's not that people have become more clever algorithm. People have gotten more clever with the joint design of the sensor and the imaging. It's not really about trying to solve a hard algorithmic problem. Examples of this would be like super resolution fluorescence microscopy and other things where I cook the physical setup to not have to solve a hard problem. This is a little bit of a hard problem. You do have some cues though, because we can look at these different images of bulging and see that this one clearly has bulging. So, one of the main cues that you have are the texture and the shading. The fact that in one image the shading is going to tell you something about the orientation of the surface. For example, if I illuminate from this direction, it will look brighter, if the surface normal matches the illumination direction. Again, for shape from illumination, you need multiple illuminations, so that method is hard to actually use. So you're really just left with the one picture. What people usually do for shape from a single picture, they use machine learning that will hopefully capture the relationship between the texture and the shape.

Q: What do you mean by textures?
A: The brightness characteristics of what you're imaging. Like, you should know that certain thing should be getting darker around the shape based on what the shape is. How much data can you collect? How many images do you think you have?

Q: It depends on how we design the device. We're still thinking of a way to actually measure, so we haven't finalized on the device itself. So we are focusing on which images we would get and how we would process them, if we were to place them in this device. When you are asking about how many images, are you talking about how many images we would get from the same angle, multiple times?

A: You sort of what a diverse data set of things you would encounter in practice, to give an accurate representation/prediction of what pediatricians may be seeing in the future. A lot of cases, patients, and different ears. If you have enough data, you could cut out the middle-man and say that you're not trying to reconstruct that 3D shape. If you have enough, you can make a guess with a computer system, but it is going to be a bit brittle and challenging. The challenges are the non-uniform textures on the surface. It's easy to figure out the orientation of a textureless object based on the way that the light hits the object. It's harder when there's texture. Here's the texture and specularity, which includes all of this mini highlights as seen in this image, for example. If you have a very matte surface like a wall or piece of paper, when light hits it, it radiates uniformly with respect to direction. So really the brightness is based on the angle at which the light hits. It doesn't depend on the viewing angle. The opposite is if you have a mirror. What you see with a mirror depends sharply on the viewing angle. What you have is a combination of the two. For shape from shaping, the matte is harder than the specular because all of these highlights are, in some sense, is unpredictable. So that's going to be a challenge. One possibility if you have enough data is to, instead of reconstructing only based on the 3D shape, i'm going to try to make a decision based on the image or patches of the image that you hand me. A good thing about a direct approach is that it will probably be less brittle. It will probably be able to use more information. For example, in this image where it's not protruding as much, there are less cues than with this other image where it's clear that there is protruding that that there is most likely an ear infection. The downside of a direct approach is that it may be hard to interpret the output. Presumably, we do this at home on my daughter with the phone using the app and the doctor wants to know rightfully how we made this decision about whether or not my daughter actually has that ear infection. If you say we made this decision because we collected 500 images and works 90% of the time, the doctor may be a bit skeptical. Even I may still want to take the kid to the doctor.

Q: So the direct approach is the analyze based on certain characteristics but you're not sure what the algorithm is doing?

A: Yes, so you might want to develop a neural network that is able to distinguish between...A neural network is a classifier that aggregates textural information in different parts of the image to make a decision. These are things that provide the best results for image classification problems. So if you were to take this image and want the computer to distinguish this is an office, this a chair, this is a table, this would be the best performing approach for that. It's biggest issue though is that it's very black box and it's a very complex classifier where you will probably not fully understand what it's doing.

Q: It's annoying in the sense that it will be hard to explain what is going on.
A: It is and it isn't. These algorithms are working drastically better than anyone would have expected, mostly due to the fact that we have more information/data. wE are in a great situation of having things that work and that we can explain. For an application like this, there may be a premium on interpretability.

Q: But the images are so different, how do we normalize it so that algorithm will accurately work?
A: The main function of this algorithm would be to acknowledge this variability. In this image classifier classes, there will be lot of images of offices and chairs and people that are very different from each other at a pixel level and different angles and lighting positions. The basic challenge is how do you build architectural settings that are invariant to things that need to be invariant, but are still sensitive enough to distinguish things that need to be distinguished.

Q: So the algorithm itself should account for that?
A: That's the hope. It's realized to some extent.

Q: How can I trust the algorithm itself to do to the classification?
A: You have dig in and have a better idea of how these algorithms work. So you have a system of layers. This is loosely inspired by what people thought the brain was doing in the 1950s. Each sequence of layers has a collection of filters that are selectively for different things at different layers. At the lower level, they are selective for little oriented textural features. In the early layers, you put your image into a feature space that is selective for certain textures. In the higher layers, it's like building up more and more complex features from the low-level features. For example, to detect a face, you're going to have features in the lower levels like orientations and higher levels will have things that are selective for orientations at different parts of the image. So, I ask about the type of data, because that basically dictates whether this type of machine learning is going to be effective or not.

Q: What would be the criteria for it to be a reasonable data set?
A: Nobody knows, that's a research question.

Q: So we just have to get as much data as possible?
A: More data is going to help. People have been working forever in computer vision on how to design systems that will help detect different objects and the viewpoint has been that not unlike what you are saying, which is that the way I should be designing a recognition system be determined by carefully thinking about what goes into recognizing an object.I'm going to top-down build a system. That was the initially the right approach, but nothing really worked. About five years approach, more of these learning based approach started getting more traction and results. The difference was data and

computation because you have many more images to work from and more processing tools and GPUs, so it's more about letting the data speak for itself. The threshold is dictated by the amount of data. If you have like images from 10 people, you should probably go with your initial approach, but you are probably going to have issues with the 3D part, especially from the shading. That's why you should re-design device to make the problems easier. If you have a lot of data, you will do better with the neural network approach.

Q: Would we have to label the data that we have?
A: You will, because you will have to label which ones have ear infections and which ones don't.

Q: We are still thinking of a way to quantify the data though.
A: You could consider assigning numbers to each image. People notice that change of going from low level to high level. What you see in low level is pretty much domain independent. The high level is very domain dependent because diagnosing ear infections is certainly not the same as diagnosing chairs. One trick to use in under sampled scenarios is using low level info that has be pre-computed from other larger data sets and applying them to the high levels that you have available. That has some potential to break the trade off. Do you want to talk about the shape from shading or the shape from another parameter? What have you been looking at?

Q: So for the bulging test, we want to focus on the shape from shading technique, but this paper has shown a lot of research about how features have been derived from other mechanisms….So the results actually quantifies the depth.
A: So the red is their predicted. Is it obvious to you that this is correct?

Q: My concern is that the eardrum is tilted in this image so wouldn't it be hard to see from just a flat surface?
A: Usually, when you a present a result in a research paper, you want to present to the reader in such a way that it's clear that you got the right answer. So, it's hard to see that it's 100% right, but it's certain lighter and darker in certain regions, except for with that random artifact.……I guess they are really discussing the height, if you turn it around, and not the depth. When I look at this image, as someone who doesn't know anything about eardrums, I feel like this is lower than that, there is a depression and this is the bottom and this is more or less the top then it curves over. It looks like there are even multiple bulges. How did they evaluate their algorithm? I feel like they haven't proven to the reader the algorithm works. It worries me because the researchers proved that they could make an image, but not how/why they were able to get this image. Therefore, it seems like this is probably going to be pretty hard to do robustly. You definitely need to read this paper again with a mind of skepticism to understand the process of implementation, since there isn't really a solid piece of evidence to prove that

there is a code the can compute hundreds or even thousands of images with the same level of accuracy and precision.….so how are they producing this image?

Q: That's explained in the methodology section.
A: How did they recover the 3-dimensional shape though?

Q: They just referred to the methodology section which conceptually discussing the shape from shade technique, which is based off of linear approximation.
A: There's a lot of code out there that will try to do shape from shading.

Q: I feel like there will be a lot of tweaking required to get those results that they computed in that paper.
A: If you're fine with that, it's just a project. If you are actually going to have people use it, then I would have some concerns because it will hard to get the code to work reliably in a hands-off manner. I think you want to make sure that you have a sufficiently diverse test set used for evaluation. As in, can you have an algorithm that can be thrown on the test set and have it work for every single image without you having to tweak and tune for every image. If that's the case, then great.

Q: After talking to you, I feel like I should look into other imaging modalities that will more likely compute more accurate results.
A: If you can choose to solve an easier problem, that's usually advisable.

Q: I guess it's a debate of what we want: reducing the difficulty of the device itself or reducing the difficulty of the processing. I feel like, no matter what the device is, there is going to be some processing that will be tricky due to the lack of dimensional information that can be collected. We've currently be focusing on ways to quantify what is seen in the otoscope. We were initially thinking of non-invasive imaging techniques that helps you figure out the depth. We were also thinking of ultrasound, which gives you a slice of the plane, but we are not sure how feasible it would be to make an ultrasound device.
A: If you want to do the otoscope, think about getting images with different illumination conditions. There is obviously a limitation with putting light through the air since there is a correlation between the medium of how the light is going to hit an object, but if there's any way to introduce a little diversity in the lighting and shading inputs, that gives you more robust information about the shape of the object because you have more information. The problem of thinking of surface orientation is ill posed.

Q: So would changing the lighting be as simple as shining different rays/intensities of lights collecting an image each time?
A: Well it can't be intensity because the thing that creates information about orientation is the angle of the light. So you are a little constrained since you are only bound to two dimensions, but adding diversity in *angle* of the light will make your problem better posed.

Q: How we create those conditions will be tricky….
A: Well I have no idea. How does an otoscope interact with the ear?

Q: I just know that it's basically a tube that goes in, you look through the device, and you'll see an image of the ear.
A: So you could choose what you put through the tube basically. It is going to be hard to generate these different angles of light if the light has to come from the tube, so any illumination is coming through, but you might be able to put a mask to change the brightness from point to point. This is called structured illumination. whenever illumination is being generated by some source and goes through an optical path that eventually lands on the ear, I could change the intensity by creating a spatially varying mask to block off some parts of the light. You wouldn't have to be too snappy about the changing/rotating of the mask. Maybe you can get the pediatrician to change five masks to make five different angles, which will all in all make the problem much better posed.

Q: I would need to do a bit more research on how that could really be implemented. So this would be more a gradient of different brightnesses.
A: This aims at an area in imaging called *phase sensitive imaging.* A camera counts photons. It tells you about the intensity of light hitting. In some sense, if i imagine that light is both a particle and a wave, that wave has a phase associated with it, what you can measure by counting is basically a magnitude, but the thing that is really directly sensitive to the depth is the phase, because if my wave is propagating and it hits and comes back, if i see farther away, i see that same thing but with a phase shift. so this consists of cooking the physical setup so that I can use the magnitude to infer the phase. This structured illumination is one of the tricks that people do, by taking more magnitude measurements than they should need to use them to try to recover the phase because the phase is more directly related to things like the height of the surface. So that's also an active area. People use it more these days for micro-scale imaging, like the imaging of live cells of high resolution, but this can be also useful for macro-scale imaging.

Value Proposition

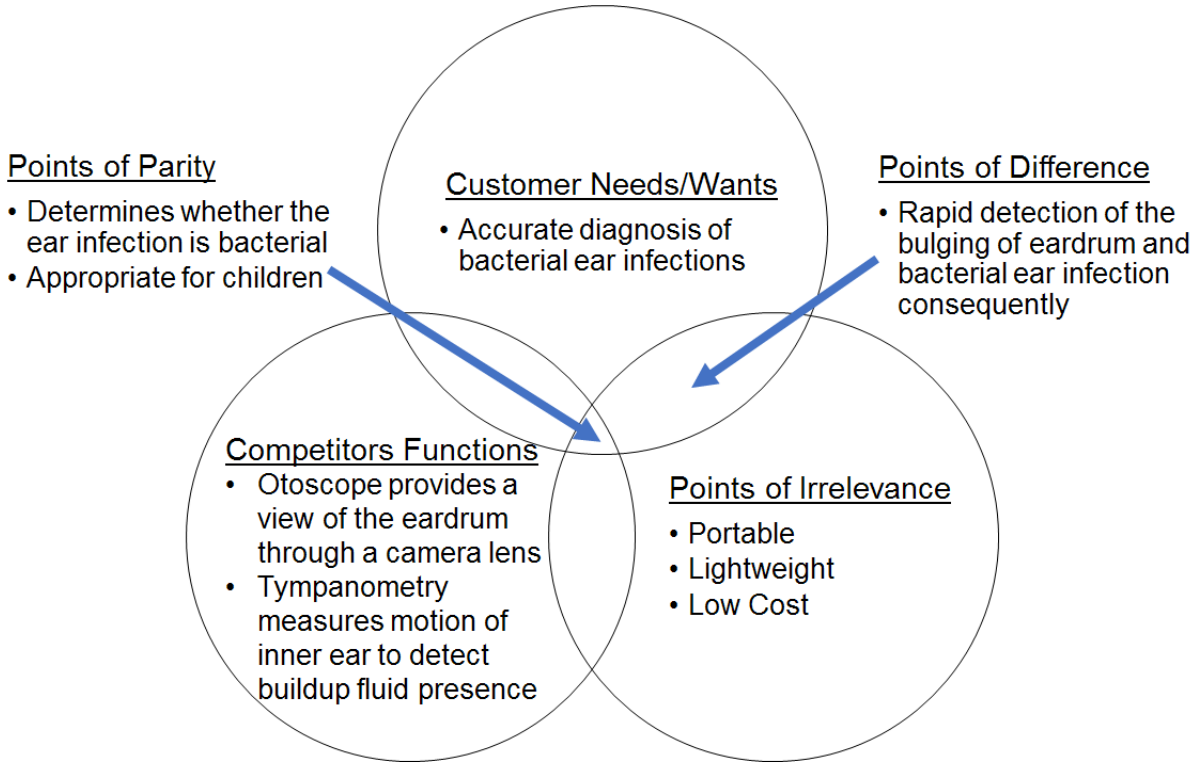


Figure 9. Venn diagram to highlight the value of proposition of the intended solution

Functional Requirements

1. Must be able to determine whether or not an ear infection is bacterial
    - The diagnosis must have a higher accuracy than the pneumatic otoscopy, which is 61% for medical residents and 77% for ENT doctors.
    - Targeting specs:
        i. Accuracy > 85%
        ii. Sensitivity > 85%
        iii. Specificity > 95%
2. Must be able to notify the pediatrician whether or not the ear infection is bacterial
    - The solution must be within one step of cycle of care

Constraint

1. Safe/non-invasive (Use same insertion practices as an otoscope)
2. Easy to use for pediatrician and/or compatible with existing practice
3. Lightweight (<0.06kg)
4. Portable
5. Affordable (35-100$)

Ideation and Brainstorming

Brainstorming Ideas

The deficits in ear infection diagnosis using current approaches have been outlined above, and the constraints and functional requirements of a new innovation have been listed. Because there is a need to obtain the results accurately, non-invasively, and rapidly, we considered the perspectives of microbiology, imaging, and data analysis.

With microbiology, we can perform a rapid test, similar to strep A test, on the fluid behind the eardrum. More specifically, it would be looking for the unique proteins produced by *S. pneumoniae* and *H. influenzae*. With that, we need to find information on what the bacteria need in order to survive and what they produce when they are surviving. We also need to find the pathogens in normal uninfected ear to serve as the background noise. However, in talking to the otolaryngologist, we found that there is no access to the fluid behind the eardrum without causing damage to the eardrum. Moreover, since bacterial infection is localized, it is impossible to find samples of the bacteria elsewhere. Therefore, this has lead us into looking for another solution.

Imaging can present information behind the eardrum. Because the ear is a fragile and sensitive organ, it is likely that we will utilize the ultrasound modality. Since we need to detect the components of the fluid (like bacteria), it also opens a door for imaging of bacterial activity (including oxygenation and concentration of products produced). The concept is similar to PET scanning which can show metabolism levels. However, imaging requires expensive instruments which can greatly increase the cost for patients.

Data analysis is the most recent idea we came across. It can render more sensitive diagnosis by integrating clinical guidelines, PubMed findings, and physical exam measurements. This can take it to the next level of accuracy by having thousands of otolaryngologist inputting their personal experience with ear infection cases. Each time we get a feedback from the doctor about the result of the patient, the system can be improved. This method will incorporate a method of quantifying the likelihood of getting a bacterial infection to optimize treatment protocols. An algorithm can be developed to give a more accurate value of quantification by using a statistical model for estimation.

Brainstorming Results

Our device must be able to rapidly determine whether or not an ear infection is bacterial with some degree of confidence. Our three prospective ideas initially included big data diagnostics, some form of imaging modality, and a cellphone accessory. Upon further examination and consideration, we concluded that a cell phone accessory consisting of all the current tools used for ear infection diagnosis would not significantly improve the cycle of care, would not differ from what is currently done, and would require some training for all individuals who purchase it. Additionally, we believed most imaging modalities would be expensive to build and to subsequently implement in clinical settings.

Thus, we had initially decided that big data diagnostics would be the most affordable and useful method for addressing ear infection diagnosis (Figure 10). This method would begin with a pediatrician inputting patient information, such as physical observations, measurements, vital signs, and images into the diagnostic tool. This information would be inputted into an algorithm that would be developed using research findings and personal diagnosis "algorithms" currently being used by pediatricians. Based on the information entered into the diagnostic tool, a probability would be generated to represent the likelihood that the ear infection was bacterial. This information would help the pediatrician decide whether antibiotics were needed depending on whether a certain threshold was surpassed. After the ear infection symptoms disappeared, the pediatrician could then input additional notes back into the algorithm, e.g. whether or not the prescribed antibiotic were effective and the believed cause of the infection. This information would then help to improve the diagnostic algorithm for future prediction. However, after further reevaluation, we saw that this prospective idea would not differ from what is currently done and might not be diagnostically reliable as it would not provide actual diagnosis but would rather make inferences based on data inputs.

Figure 10. Block diagram of the prospective big data diagnostic method for ear infections

Thus, we concluded that a device that implemented alternative imaging methods such as acoustic reflectometry, in combination with an algorithm that used the obtained measurements along with other physical factors would be better able to quantitatively predict the likelihood of having a bacterial infection.

Concept Screening and Scoring

Possible Solutions

Our initial prospective solution was a device resembling a pair of over-the-ear headphones that predicts the likelihood of having a bacterial ear infection by collecting the following measurements in a non-invasive manner (Figure 11, Figure 12):

- Viscosity of the fluid behind the eardrum
- Eardrum bulging and transparency

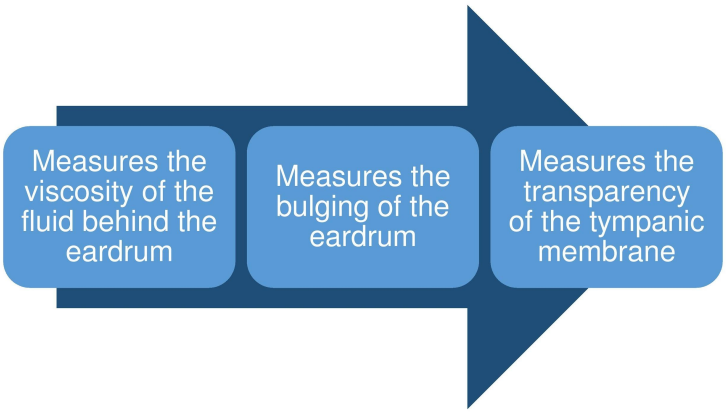


Figure 11. Flow chart illustrating the three primary functions of our prospective solution

Figure 12. Over-the-ear prototype of prospective solution with an integrated camera for image acquisition (left) and a circuit system to test for fluid viscosity (right). Although shown separately, both components will be included together on both sides of the device.

These measurements were chosen because the severity of these symptoms and the presence of bacterial AOM are highly correlated. A bulging eardrum is highly associated with the presence of a bacterial pathogen, with or without a concomitant viral pathogen. It is reported that a bulging eardrum has positive bacterial cultures 75% of the time, this number increases to 80% if the eardrum is yellow and non-transparent [2]. In middle ear fluid, the viscosity differs between a bacterial or viral ear infection. The cutoff viscosity needs to be tested in order to understand the accuracy required for this measurement.

Each measurement is obtained through different mechanisms that serve as different parts of our device's circuitry. The viscosity of the fluid present behind the eardrum will be measured through acoustic reflectometry, while eardrum bulging and transparency will be calculated from an image

of the patient's eardrum. Although a camera addition to our device makes it more intrusive, we found this method to be cheaper than ultrasound and other imaging modalities. Nevertheless, we may have to consider ultrasound if the camera approach fails to produce significant results.

Lastly, the device will implement an algorithm that uses the two measurements in combination with age and other physical symptoms (e.g. body temperature) to predict the likelihood of having a bacterial infection. When a patient pays a follow-up visit, the healthcare provider can input an updated diagnosis (such as current symptoms or ear infection has been resolved), which will then serves as training data and improve our algorithm's accuracy.

Concept Selection Matrices

Concept Selection Matrix		Reference Doctor Diagnosis		Big Data		Imaging		Phone Accessory	
CRITERIA	WEIGHT	*Score*	Weighted	*Score*	Weighted	*Score*	Weighted	*Score*	Weighted
Accuracy	4	3	12	5	20	4	16	3	12
Speed	4	3	12	4	16	4	16	4	16
Invasiveness	4	3	12	3	12	5	20	3	12
Training	2	3	6	2	4	2	4	2	4
Cost	2	3	6	2	4	1	2	4	8
Convenience	1	3	3	5	5	2	2	5	5
	totals:		**51**		**61**		**60**		**57**

Figure 13. Concept selection matrix for the big data, imaging, and phone accessory solutions

Based on our concept selection matrix, big data diagnostics and an imaging modality yielded the highest scores of 61 and 60, respectively (Figure 13). The three most important criteria for our solutions were accuracy, speed, and invasiveness, while amount of training required, cost, and convenience were all deemed less important. While big data diagnostics earned the highest score as our top prospective solution we opted for an alternative imaging modality because it has the potential to be accurate, quick, and convenient.

Proof of Concept for Viscosity Measurement

Principle of Operation for Spectral Gradient Acoustic Reflectometry

The Spectral Gradient Acoustic Reflectometry (SG-AR) is a technique that determines the probability of the middle ear fluid effusion by measuring the mobility of the tympanic membrane. More specifically, SG-AR measures the response of the tympanic membrane to a sound pulse of frequency spectrum between 1.8 and 4.4 kHz [37]. The technique relies on the principle of partial cancellation of emitted sound by sound reflected back from the tympanic membrane [36].

The speaker sends the sound pulse through a source tube past a microphone into the ear canal. This emitted sound propagates down the ear canal and a portion of it is reflected back from the tympanic membrane. The microphone and the tympanic membrane are close enough so that emitted sound (i.e. the incident sound) and its reflection (i.e. the reflected sound) are superimposed. The reflected sound is variably out of phase with the incident sound, resulting in the partial decrease in sound pressure as measured by the microphone [36]. A nadir in sound

pressure is the point of maximum nullification. It occurs at a frequency for which the reflected sound is 180 degrees out of phase with incident sound.

Reflectivity is a measure of sound pressure and it is calculated as the ratio of the superimposed signal (refer to as the reflected signal) to the incident signal/sound. A tympanic membrane that has fluid behind will cause more sound to be reflected and the nadir to be in a narrower band on the frequency versus reflectivity plot. The spectral gradient angle (SGA) measures the angle created around the nadir. This spectral gradient analysis has been found to be highly correlated with the probability of middle ear fluid effusion [37].

Hypothesis and Rationale

Since acoustic reflectometry has been used to examine middle ear fluid, we want to apply the SG-AR technique to see a correlation exist between the viscosity of middle ear fluid to the spectral gradient angle. The viscosity of middle ear fluid is correlated to bacterial ear infection. It has been found that higher the viscosity of middle ear fluid, the more likely it is an bacterial infection. Bacterial infection creates purulent fluid and it has a range of viscosity from 1000cP to 8000cP [34]. Whereas viral infection creates serous fluid which has a viscosity on the order of hundred cP which is much lower than 1000 cP.

The question we would like to address is: does the change in fluid viscosity behind the eardrum have an impact on sound reflectivity (measured by spectral gradient angle)? More specifically, would a higher viscosity result in a sharper spectral gradient angle measured by the SG-AR? Our hypothesis is that it will. The rationale is followed: higher the viscosity of the fluid behind the eardrum, lower the mobility of the eardrum, thus a sharper spectral gradient angle measured by the SG-AR. A sharper spectral gradient angle relates to more sound reflected off the membrane as well as low eardrum motility [28]. We know that pus produced from bacterial infection has higher viscosity (over 1000cP), and we want to relate a low mobility of the eardrum to a higher viscosity behind it. If we can do that, we can use acoustic reflectometry to indirectly measure the viscosity behind the eardrum and relate that to the likelihood of a bacterial ear infection.

Experiment/Testing Methods

To conduct our acoustic reflectometry experiment, we first built an infected ear model chamber (Figure 14) that included materials resembling the tympanic membrane and ear canal. We chose to model our chamber using known average dimensions of the middle and outer ear and to use cellophane for our membrane because of its flexibility and similarity in properties to the actual ear wall. The ear canal was modeled using a polypropylene plastic. The infected ear model chamber had a volume of approximately 2 cm^3. We varied the viscosity of the fluids used to fill the infected ear model chamber, starting off with sugar water solutions of 0g (30.3 cP), 10g(53.1 cP), 20g(70.5 cP) and 40g(88.4), and proceeding to test motor oil SAE 40 (453.8 cP), castor oil (1699.9 cP), and karo syrup(7000 cP).

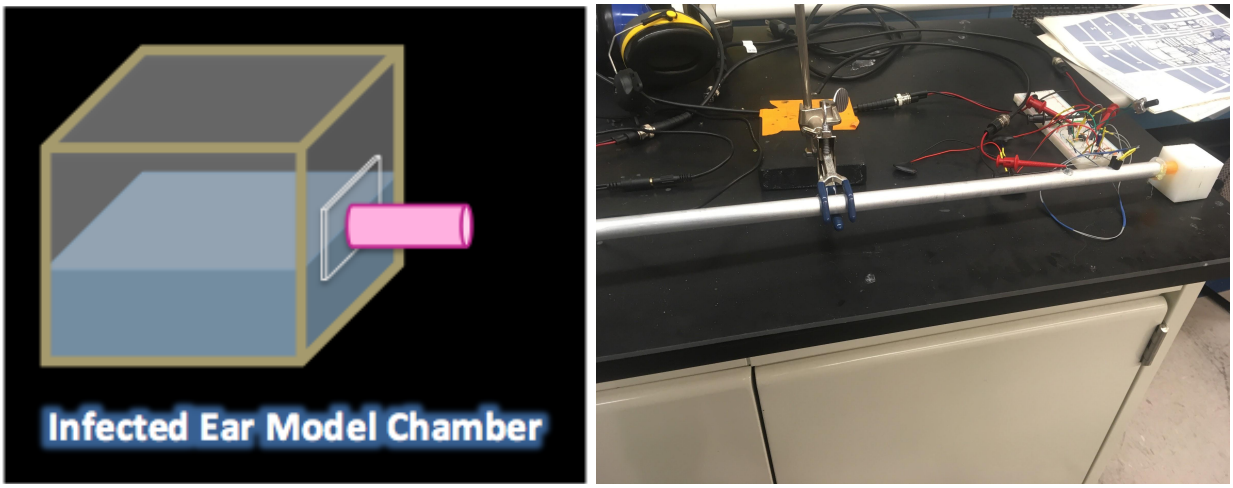


Figure 14. Schematic (left) and actual (right) infected ear model chamber for experiments

We also built a simple acoustic reflectometer that emits the sound and collects the output signal. The circuit contains a microphone (1 uF capacitor), bandpass filter (3.3 kOhms 5% for high pass resistor, 33 Ohms 5% for low pass resistor, and 0.47 uF capacitors), and amplifier to transmit and record a sound wave. See Figure 15 for the schematic of this circuit. Individual sound pulses from 1.8- 4.4 kHz in steps of 100 Hz are created in MATLAB. The speaker emits the sound into a source tube. The superimposed signal (cancellation of the incident sound its reflection) is collected by the microphone. The source tube is approximately 65 cm with one end placed partially inside the ear canal. Both the microphone and the speaker are placed on the source tube and their location is about 5 cm away from the tympanic membrane.

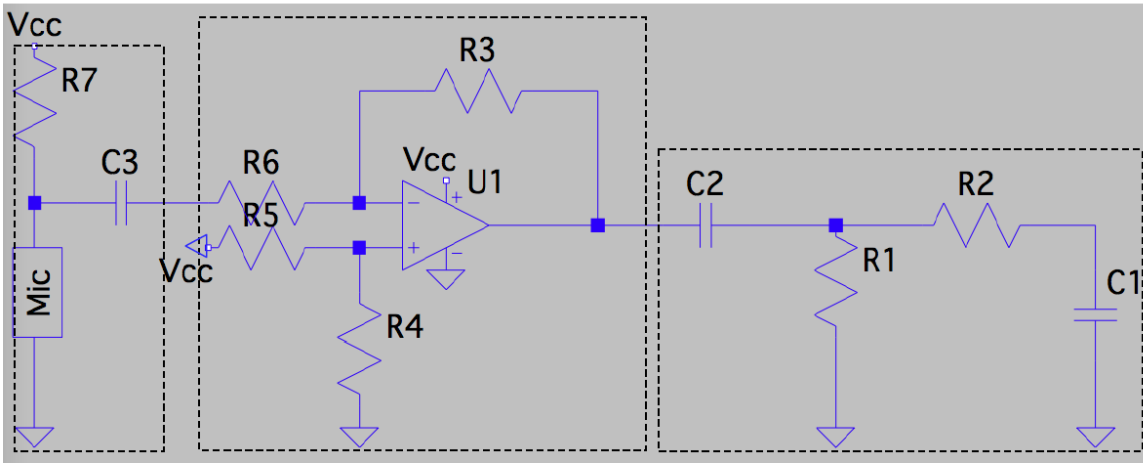


Figure 15. Schematic of the circuit built for the acoustic reflectometry experiment

The incident signal was collected using the long source tube with a sound cancelling material called rock wool at one end and the speaker at the other. The source tube was long enough for the initial pulse to be passed and recorded the microphone by the time any reflection can bounce back to it. This was done at all frequencies and later compared to the superimposed signal.

To begin the experiment, the chamber was filled with 5 mL of fluid of interest. We sent a sound pulse of one frequency (with value between 1.8-4.4 kHz) and recorded the superimposed signal. We found the peak-to-peak value and the energy (for which one the first copy of the reflection is considered). The reflectivity is computed in two ways. One is by taking the ratio of the peak-to-peak value in the incident and the superimposed signal. The other is by taking the ratio of the signal energy. This creates one point in the reflectivity versus frequency plot. Next, we sent a sound pulse of another frequency and repeated the whole procedure to populate the reflectivity versus frequency plot from 1.8-4.4 kHz at a resolution of 100 Hz. To measured the spectral gradient angle, we selected a region to the left of the nadir and region to the right of the nadir. Then, we performed linear regression of the data points in these regions to find the slope. The results of linear regression is shown by the thick lines in Figure 20. We used the slope from the linear regression to compute the spectral gradient angle.

We performed the procedure described in the paragraph above and determined the spectral gradient angle for each fluid. For each liquid, we conducted three trials. The spectral gradient angle was plotted versus the fluid viscosity. We also looked for any other trends in the data we could use to correlate to viscosity.

Results

Figure 16 shows the recording of the incident signal and the superimposed signal. There is a tail in the superimposed signal (right plot of Figure 16). This indicates that there is imperfect absorption of reflections at the end of the source tube.

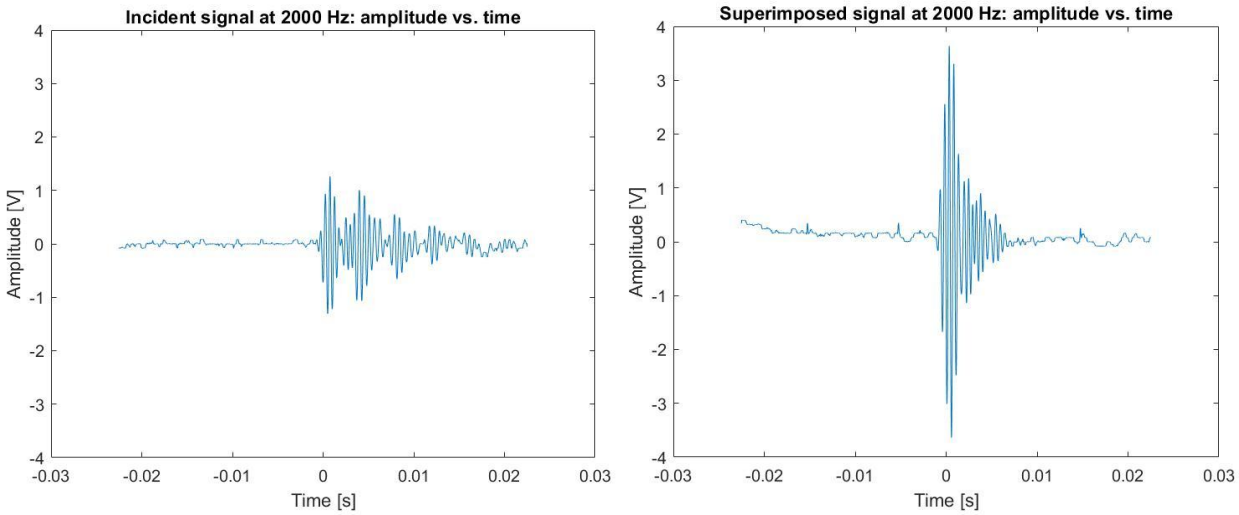


Figure 16. The amplitude versus time at an input frequency of 2000 Hz. Left: incident signal. Right: superimposed signal for karo syrup.

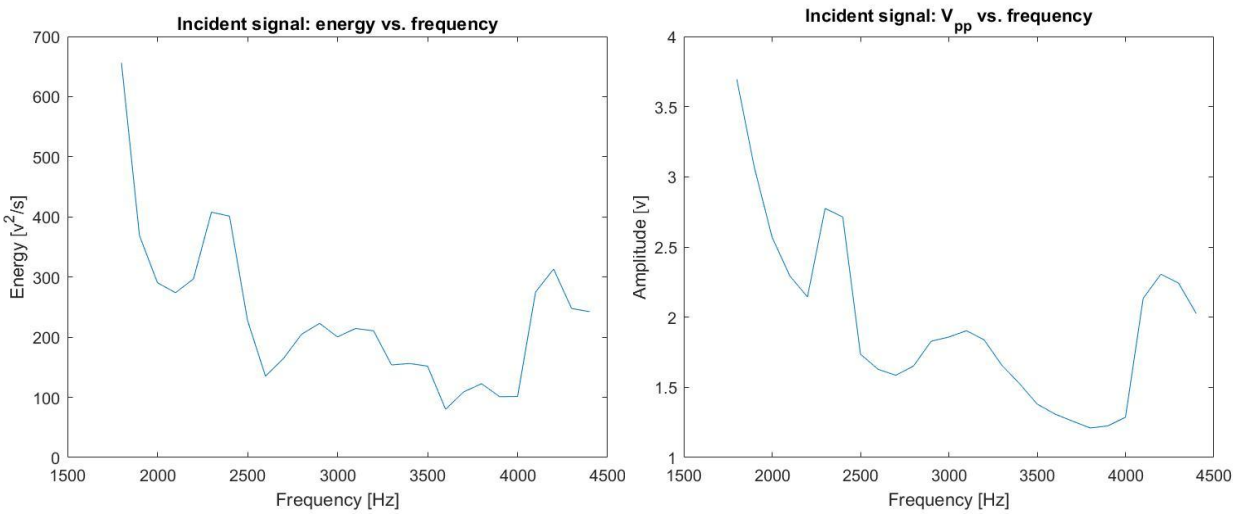


Figure 17. Left: the energy of the incident signal as a function of frequency. Right: the V_{pp} of the incident signal as a function of frequency.

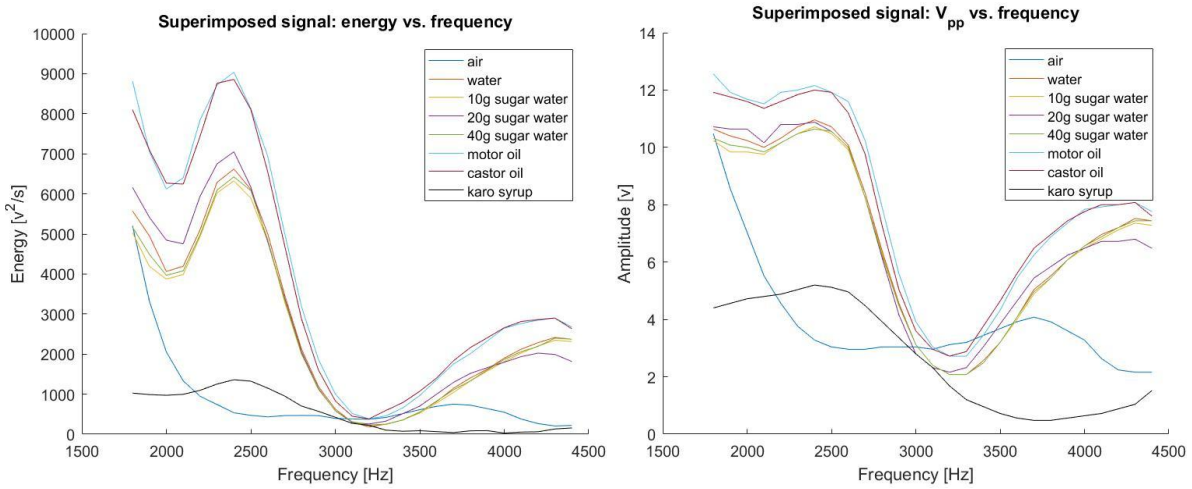


Figure 18. Left: the energy of the superimposed signal as a function of frequency. Right: the V_{pp} of the superimposed signal as a function of frequency.

Figures 17 and 18 show the the values used in the calculation of reflectivity and the two types of reflectivity values are shown in Figure 19. The way of obtaining them is described in the Experiment/Testing Method section. We are able to see a nadir at around 3.2 kHz in the reflectivity plot computed from the ratio of energies. Therefore, the spectral gradient angles are extracted from the reflectivity calculated from the ratio of energies. Figure 20 shows an example of a reflectivity vs frequency graph that was used to find the spectral gradient angle (SGA).

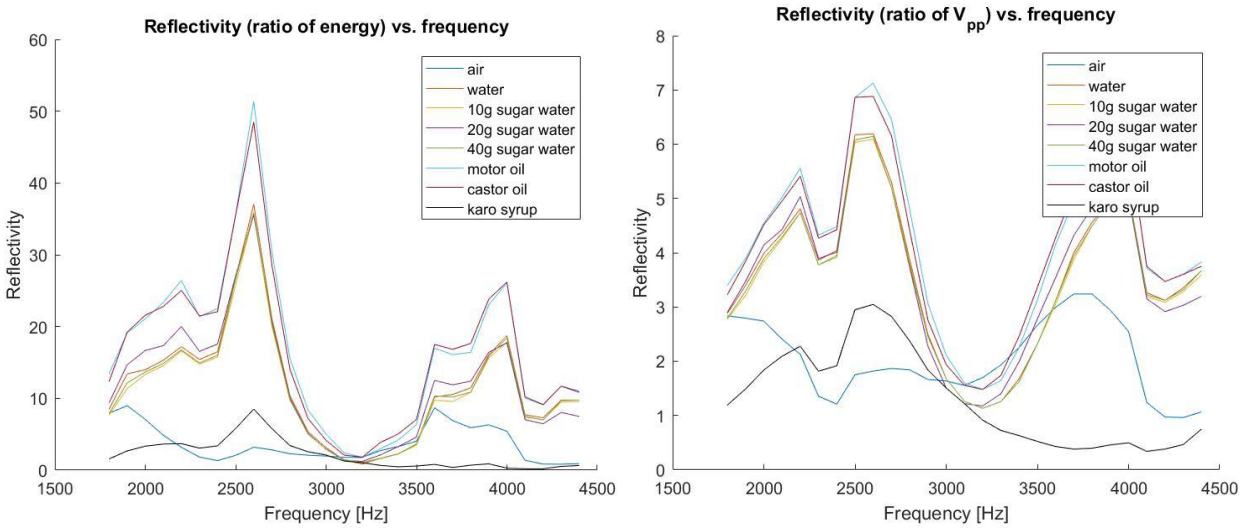


Figure 19. Reflectivity as a function of frequency.
Left: Reflectivity is the ratio of the energy of the superimposed signal and the energy of the incident signal. Right: Reflectivity is the ratio of the voltage peak-to-peak (Vpp) of the superimposed signal and the Vpp of the incident signal.

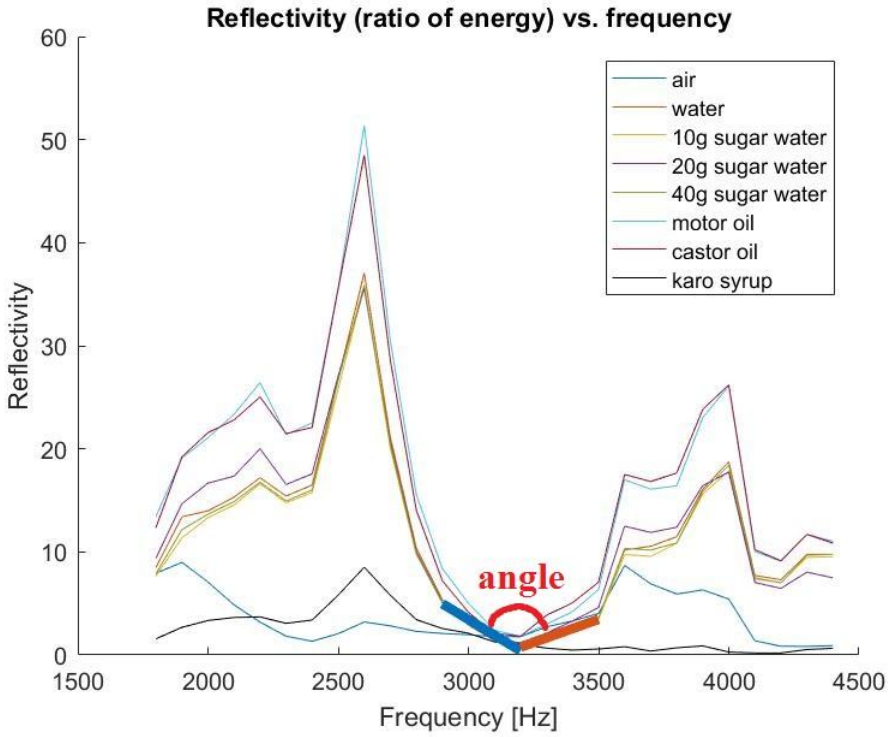


Figure 20. Reflectivity as a function of frequency with water's spectral gradient angle.

Water had an SGA of 128.8 degree, 10g solution has an SGA of 133.6 degree, 20g solution has an SGA angle of 127.6 degree , 40g solution has an SGA angle of 107.5 degree , motor oil has an SGA of 107.5 degree, and castor oil has an SGA of 109.7 degree. Karo syrup doesn't have a

measureable SGA. These values are plotted against the solution's viscosity (Figure 21). The low viscosity solutions (water and sugar solutions) have a larger angle compared to that of the high viscosity solutions (motor and castor oil). However, this trend is not observable at a finer viscosity scale. That is to say, there is no relationship between angle and viscosity between the sugar solutions, nor does it exists between the oils.

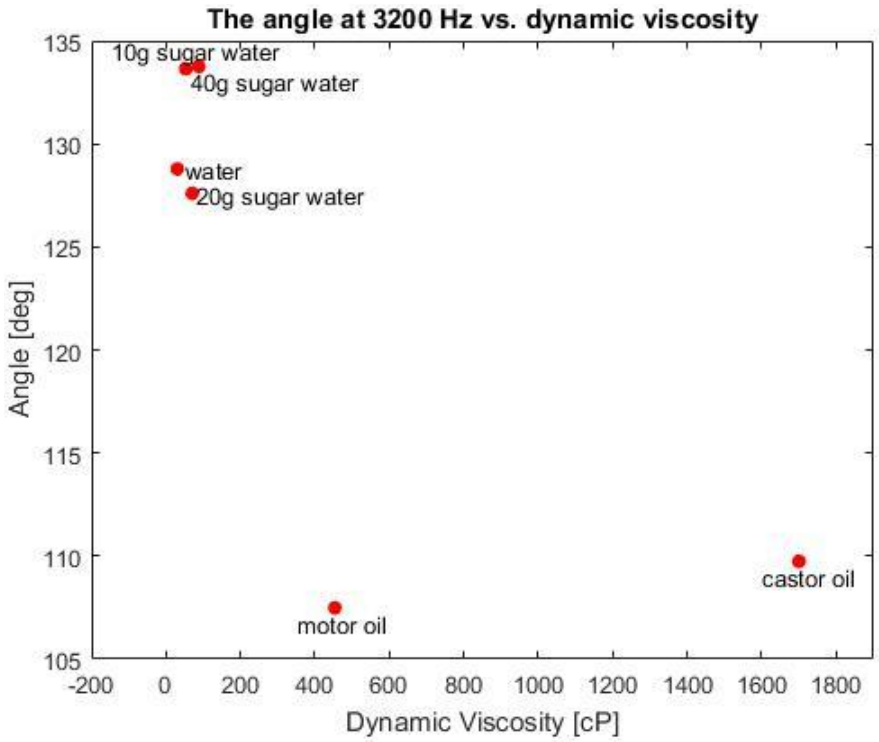


Figure 21. Plot of the spectral gradient angle for different liquids vs dynamic viscosity

We have also looked at the other trends in the reflectivity plot including the maximum, the area under the curve and the difference between the maximum and minimum. None of those demonstrates a correlation with the viscosity.

Conclusion

We can observe a rough correlation between the spectral gradient angle and the fluid viscosity. The spectral gradient angle increases as the viscosity of the fluid increase. However, if we only look at the sugar solution data, this correlation does not hold. The difference between the sugar water viscosity is smaller compared to oils. This implies that the acoustic reflectometry method and the setup we used are unable to provide information on the correlation between spectral gradient angle and viscosity on a finer scale. This is either because of the hypothesis is inherently incorrect or the setup is not perfect enough. We conclude that the data we obtained is not sufficiently accurate to be considered useful for the pediatrician.

We did research on other possible methods to accurately measure viscosity in an indirectly manner. The only other method would be ultrasound, but that is expensive and requires the ear

to be filled with sterile fluid. The need for a seal on the ear and sterile fluid keeps ultrasound from being a pediatrician prefered method in diagnosing AOM, and solving that issue would be a separate project in itself. Because of these issues we've decided to drop the viscosity measurement from our device and focus on bulging.

Proof of Concept for Bulging Classification

We examined two methods that could potentially relate the degree of bulging to a quantitative measurement: shading gradient method and support vector machine (SVM) classification.

Shading Gradient Method

Creation of Colormaps

Since bulging of the tympanic membrane is specific to bacterial AOM, we decided to take advantage of the laws of light on a bulging (concave up) surface to analyze shading gradient. We tested this method under the assumption that the more bulging a surface has, the closer the surface would be to the light source, creating a more concentrated area of white light in the image. The more bulged a surface is, the more likely there would be differences in white light across the areas of the tympanic membrane. Areas that are mostly flat, however, would receive less light than bulged areas, thus creating a colormap from differences in light and shading.

To create a colormap, we first had to obtain an image of the eardrum using the ENTO camera. The user outlines the eardrum from the obtained image in order to specify the region of interest for a better comparison of shading area. The MATLAB code is run to create a color gradient map that uses five colors. The proportion (p) of each color in the outlined area is computed by MATLAB

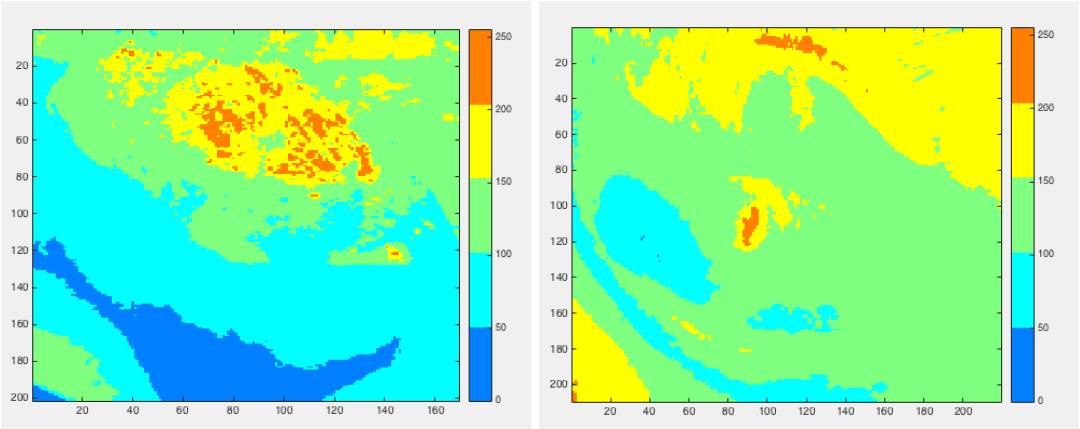


Figure 22. Resulting color gradient maps of selected regions, using shading gradient method. Left: result from a bulging eardrum image. Right: result from a non-bulging eardrum image.

Scoring of the Color Gradient Map

A score is assigned to the color gradient map in order to return a quantitative result that indicates the degree of eardrum bulging. The following formula is used to score the color gradient map returned by the shading gradient method:

$$Score = 255 \times p_{orange} + 204 \times p_{yellow} + 153 \times p_{green} + 51 \times p_{cyan} + 0 \times p_{blue}$$

where *p* is the proportion of the respective color in the colormap. The constant in front of *p* is a preassigned weight for each color. This score is compared to the average bulging threshold of all the bulging and non-bulging training images that determines whether or not the eardrum is bulged or not. If it is bulged, then there is a high likelihood that the ear infection is bacterial.

Results and Conclusions

The score distribution for the bulging and the non-bulging groups is represented by the mean and variance. The average score for the bulging images in the library is 24.15 with a standard deviation of 15.22. The average score for the non-bulging images in the library is 12.21 with a standard deviation of 10.99. We performed a *t* test to compare the score of a test image to these two groups. The results will indicate whether or not the test image is drawn from the same distribution as the one of the groups. In other words, the results obtained from the *t* test distributes the test images between the two groups.

Note that 72% of the test images (N = 18) were correctly sorted into the group that they were originally placed in. This outcome is less optimal than what we anticipated and desired. The distribution of the bulging and non-bulging also overlapped due to the small number of images in our eardrum library. The underlying assumption that the bulging and non-bulging groups have different distributions does not hold true in this method. Thus, a test image could be sorted into both groups, thus making the score meaningless.

Support Vector Machine (SVM) Classification

Principle of Operation

The goal is to classify the bulging of the eardrum because knowing the degree of bulging provides information about the likelihood of a bacterial ear infection. The camera takes a picture of the eardrum. This image is then sent to the classification algorithm, which will output either a normal eardrum, a moderately bulged eardrum or a severely bulged eardrum. Instead of directly taking images using the ENTO camera, an image library was created from public online databases. The library was split into a test set and a training which were consequently used in the algorithm for classification.

Understanding the advantages and disadvantages of SVM is important in the selection of a machine learning method. The advantages of SVM include categorical predictor support, large memory usage, easier to interpret, and easier algorithm to construct. For these reasons, we choose SVM to construct a classification algorithm.

Here is a brief summary of what happens in a SVM classification algorithm. Each image carries a set of information. Images in the training set are labeled according to their category. SVM finds the hyperplane or the line that best separates the two categories by comparing the information between the categories. support vectors are defined as the points closest to the hyperplane. The algorithm returns a score for each image based on its relationship to the hyperplane. When the user inputs new images into the algorithm, the image will be assigned to a category based on this score.

Results and Conclusion

Images of normal eardrum taken by the camera were added to the library, which also consisted of images of bulged eardrum images posted by other research group online. Figure 23 shows some sample images from the library and the respective scores calculated by the SVM algorithm. Most of the bulging eardrums received higher and positive scores than the eardrums. While most of the non bulging eardrums received negative scores.

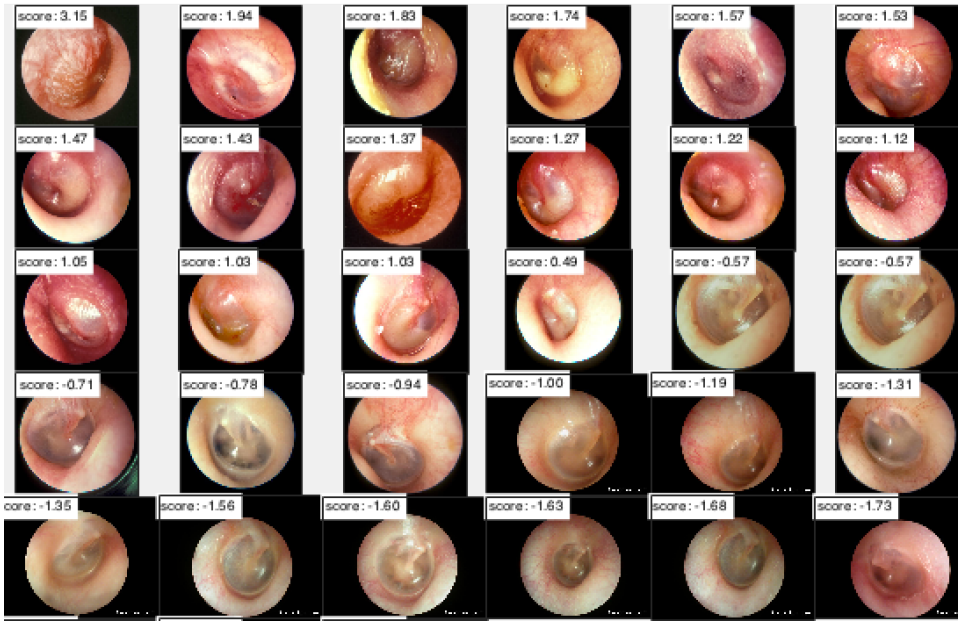


Figure 23. Sample images from library and their associated SVM scores.

ROC curve is a plot that illustrates the performance of a binary classification system. The curve is created by plotting the sensitivity (or the true-positive rate) against the fall-out (or the false positive rate) at various threshold settings. Sensitivity is defined as number of true positives over the number of positive samples. Fall-out is defined as the number of false positive over the number of negative samples.

Table 3. Terminologies used in performance evaluation and their meaning in the context of bulging eardrum.

Terminology	Meaning
Positive samples (P = TP+FN)	Eardrum image identified as bulging by SVM
Negative samples (N = TN+FP)	Eardrum image identified as non-bulging by SVM
True positive (TP)	Eardrum image that is bulging in reality
True negative (TN)	Eardrum image that is non-bulging in reality
False positive (FP)	Actual bulging but identified as non-bulging by SVM
False negative (FN)	Actual non-bulging but identified as bulging by SVM
Sensitivity = recall = TP/P	Probability of detection
Fall-out = 1 - specificity = FP/N	Probability of false alarm
Precision = TP/(TP+FP)	Positive predictive value

In our case, there was a few false negatives, in other words, an image that has a bulged eardrum was classified as non-bulging, causing the accuracy to decrease by 6% and change the shape in the ROC curve, as seen in Figure 24. Despite the false negative, the algorithm has an average precision of 94% and this accuracy value is still higher than that of a pediatrician.

Precision and recall curve is another measure of the performance of a binary classification algorithm. We desired a high average precision, which was observed (Figure 25). The resulting curves mimic that of a perfect model, which would be seen when there are no false positives or negative. In other words, most of the image were accurately assigned to bulging or non-bulging, based on the training library of images. This suggests that SVM has a potential to accurately classify eardrum images.

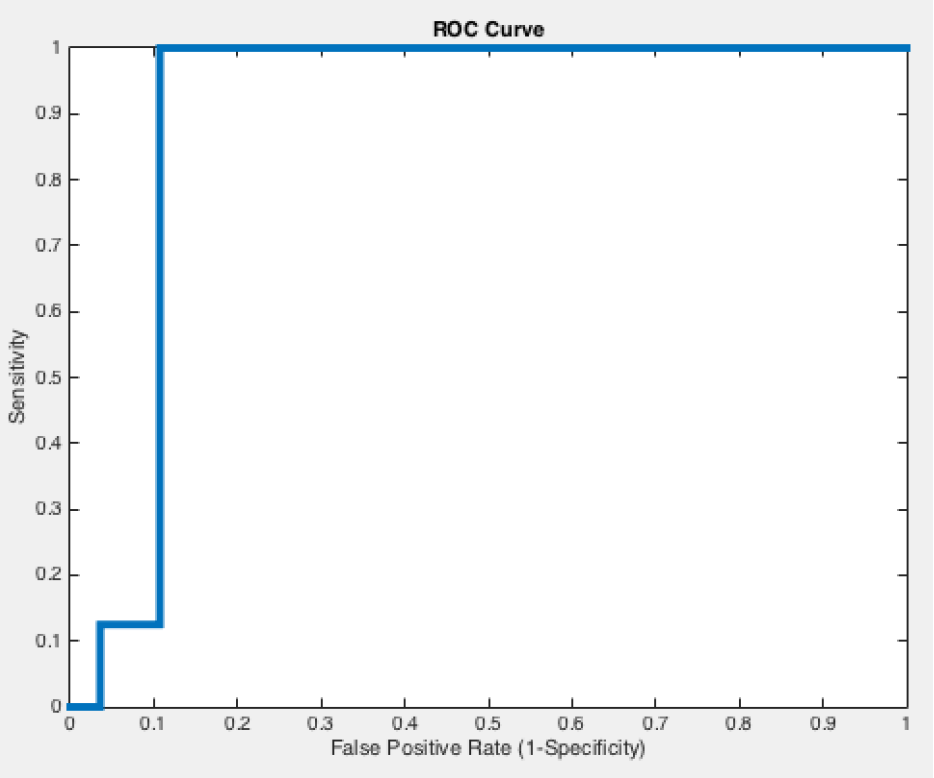


Figure 24. Receiver Operating Characteristic Curve (also known as the Sensitivity vs. Specificity Curve)

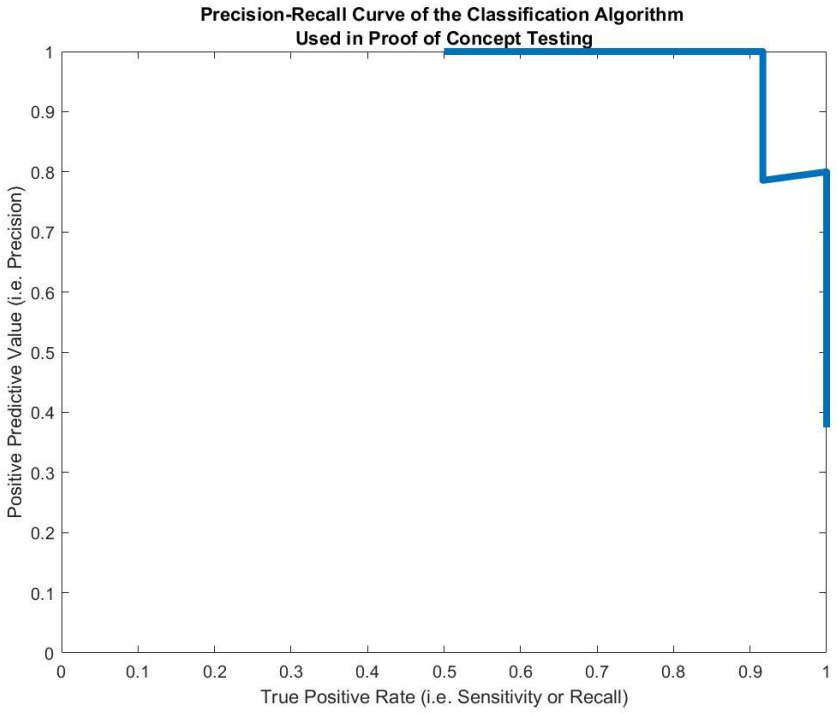


Figure 25. Precision-recall curve of the classification algorithm used in the PoC testing.

The First Prototype - AURI

How It Works

The updated solution only retains the bulging measurement, or most specifically, the classification of the degree of eardrum bulging. We discards the earphone design and implemented AURI. AURI resembles an otoscope (Figure 26). It has a spherical handle and a standard speculum which goes into the ear canal. The camera is inside the black speculum, which is secured onto the spherical handle by a ring. Figure 27 shows the components in AURI and Figure 28 shows two sample images taken by AURI.

Figure 26. The first prototype AURI (excluding the controller).

Figure 27. The components in AURI. From left to right are the controller/processor, the camera, different sizes of speculum, the ring for securing the speculum onto the handle, and the handle.

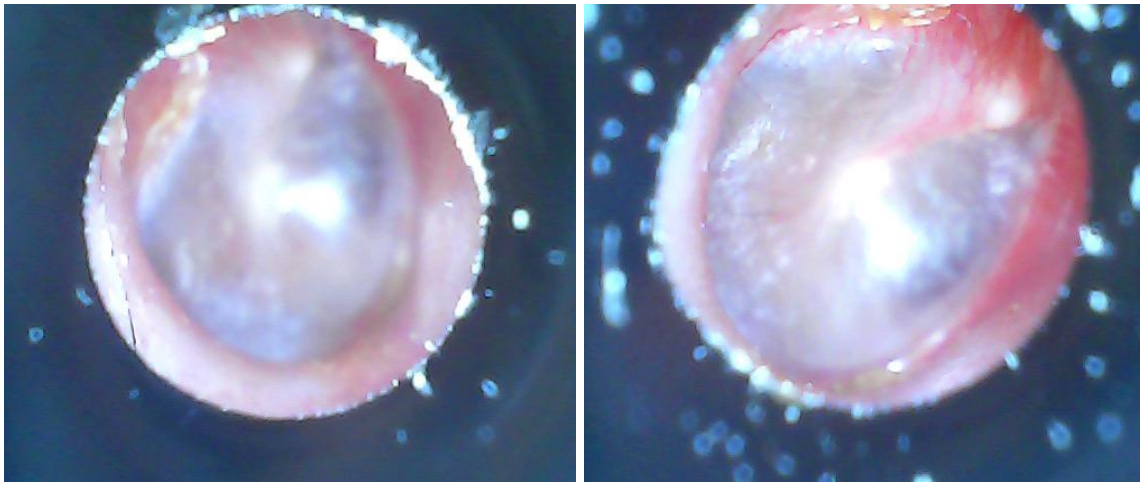


Figure 28. Sample images taken by AURI.

The steps of how AURI functions are outlined in Figure 29. A controller powers up the camera. The spherical handle of the device is used to align the eardrum with the camera. Our camera will take the image and then send it to the classification algorithm. The algorithm will return the category (ie. the degree of bulging) that the image belongs to. Lastly, the results will be displayed on the screen of the controller.

Figure 29. The flowchart of how AURI works.

Performance Testing with Multi-class SVM Classification

Since the degree of bulging has multiple categories (normal, moderately bulged, and etc.), we need a multi-class SVM for classification of images. We employed histogram of gradient (HOG) to define the support vectors in SVM. It is a common technique used in multi-class SVM. In essence, images are split into blocks, the distribution of gradient orientations in each block is calculated and served as support vectors for SVM.

The images in the library were cross-validated to determine whether the results match the original categories of each images. Cross-validation returns an accuracy of 97.7%, 78.6%, and 14.3% for the normal, moderate, and severe categories respectively, as seen in Figure 30.

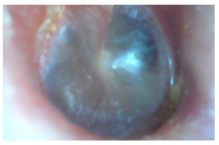
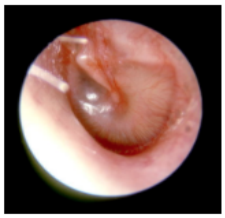
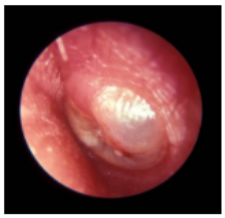
	Accuracy
Normal: 	97.7%
Moderate: 	78.6%
Severe: 	14.3%

Figure 30. A sample of images from each category and their corresponding accuracies.

The accuracy was low for the severe bulging case because a lot of the severe bulging images were labeled as moderate bulging. In other words, the number of false positives are high, resulting in a low sensitivity. This may have been attributed to the size of severe bulging image library being small. Our whole library consists of only 66 images so far. There are much more images in the normal category than in the moderate and the severe category. For this reason, there are less information for the algorithm to collect on the severe bulging case; and the algorithm is more likely to assign bulging image to a normal category which may contain outliers that match the features in this bulging image. As a result, the accuracy of the algorithm for this category decreases.

We calculated the the average accuracy levels 1) with all the categories and 2) without the severe category, which had the lowest accuracy. The resulting averages for the were 82.1% and 92.3%, respectively, as predicted. These results show that the severe category is currently the least accurate due to the shortage of images. In the next stage of the prototyping, the team is striving to improve the performance of classification algorithm by collecting more images of severe bulging and testing on other more robust algorithm such as neural network.

The Second Prototype

Updates

Hardware:

The core of our new prototype is the Raspberry Pi 2 instead of a laptop. This was done to shrink the size of our prototype and make it portable. Consequently, a new camera, lighting system, and battery were needed to replace the ENTO camera and laptop. Moreover, a new monitor was needed to display a live-feed from the camera (Figure 33).

Software:

A major change in the approach for detecting bacterial AOM was made in the software of AURI. Our prototype now utilizes a convolutional neural network algorithm instead of HOG to extract features from acquired images for SVM classification (Figure 31).

Rationale:

We tested the performance of the multi-class classification to differentiate between the normal eardrum and different degrees of bulging. However, the performance was far below the target specifications of our product. We attribute this non-ideal performance to a small library size. The required size for such a library is on the order of thousands, but a minimum of a hundred would do for proof-of-concept. Our library consists of only 70 images though due to copyright issues. Since our library does not have enough images to successfully categorize different degrees of bulging, our overall performance suffered.

To improve our classification system, we went back and reexamined our approach for classifying eardrum bulging. Our previous research showed that bulging is an indicator of bacterial AOM. This means that the ability to distinguish between a bulging eardrum from a normal eardrum is sufficient for an accurate diagnosis of bacterial AOM. The ability to determine the severity of bulging is interesting information to have but unnecessary for the problem we are addressing. When more images are obtained in the future, we can consider adding this feature back to increase our confidence in the diagnosis. Thus, our most recent prototype uses binary classification to correct for the poor results obtained from multi-class classification.

How It Works

AURI shows a live view of the eardrum and allows the user to take an image of the ear, that image is sent to a local server, which performs a classification algorithm. In this algorithm, features are extracted from that image, those features help determine how SVM classifies the image. Lastly, the results are then sent back to the device where an LED will light red or green depending on the outcome.

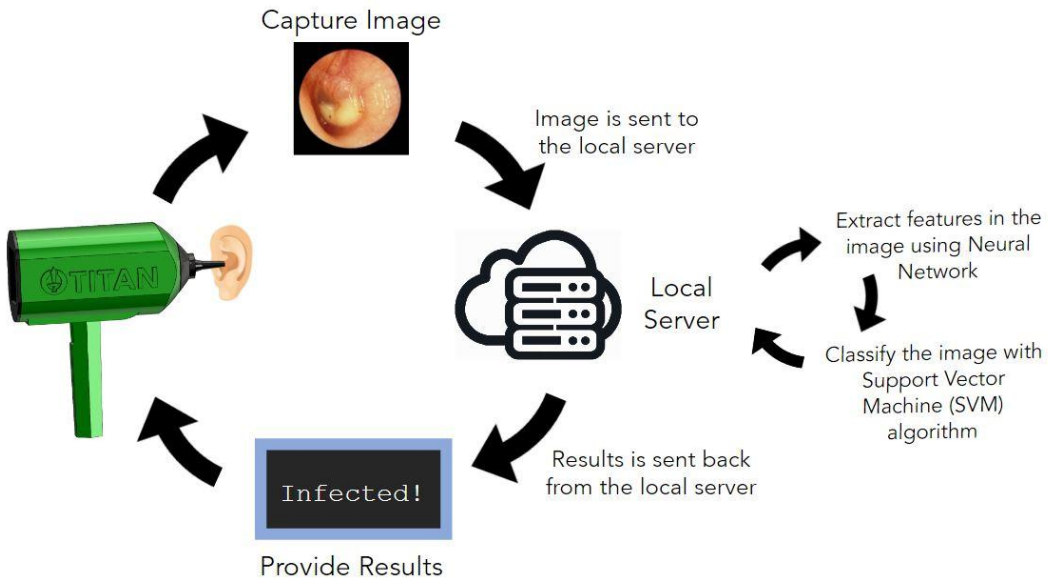


Figure 31: Overall process of the device.

Figure 32. The components in the final AURI prototype. From left to right is the final prototype, the ear specula securing ring, disposable ear specula of different sizes, the Raspberry Pi Spy Camera, the Raspberry Pi processor, the display monitor, and the rechargeable battery.

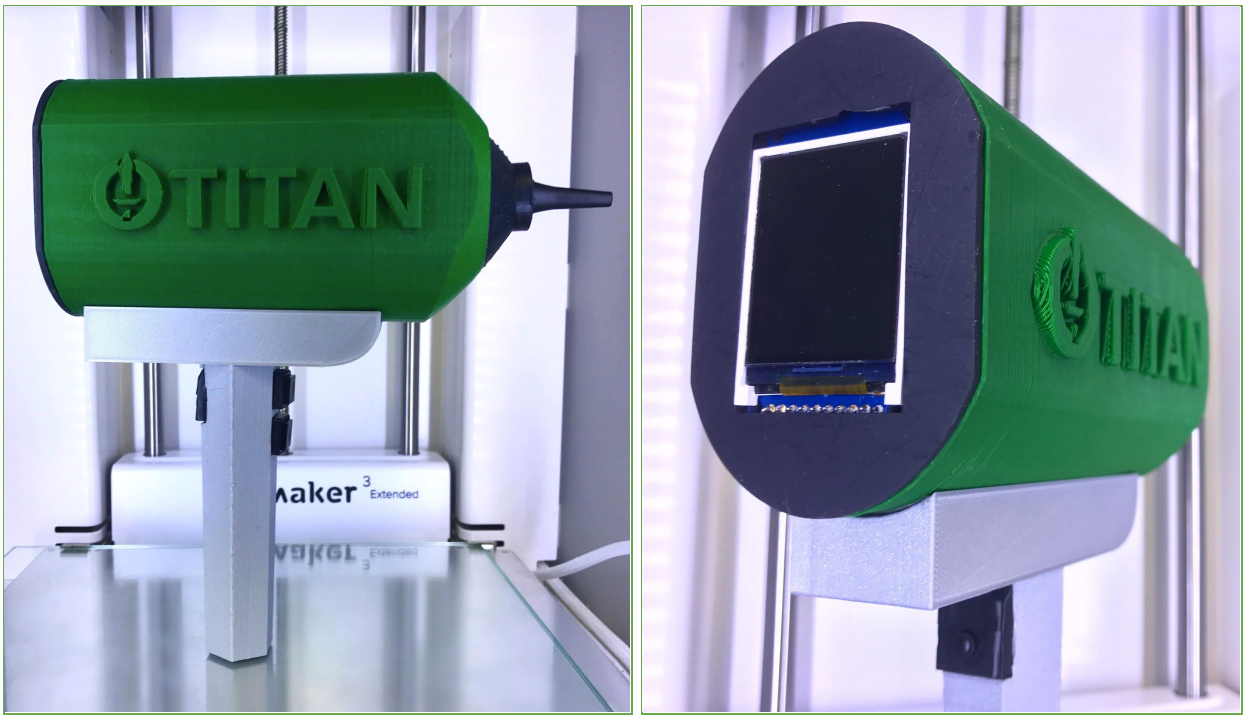


Figure 33. Images of the constructed final prototype (left) with the display monitor on the back side (right). The final AURI prototype includes a photo acquisition button, a reset button, and a light switch on the handle of the device.

Algorithm Overview

The algorithm contains a feature extraction part and a classification part, where the classification was trained with an image library consisting of 70 images. Training our algorithm using such a small dataset lead to a low accuracy and specificity. To overcome this we used a pre-trained deep learning Convolutional Neural Network (CNN) to train the algorithm. This allowed us to extract high level features from our small image set. For this, we used Google's open source pre-trained CNN TensorFlow.

A Convolutional Neural Network is a complex multilayered learning algorithm that uses convolution of an image and filter to turn low level physical features like a curve or edge into mathematical ones. It will then pool those features into subcategories to provide nonlinearities and robustness to the system before performing another convolution. Each convolution will then be able to identify higher level features than the previous step. By the time we are able to detect high level features like a hand or paw we can proceed to the final fully connected layer. This layer takes volume input from the layer before it and provides a number N which represents the number of categories the program can separate an image into. The CNN also assigns the likelihood that certain high level features correlate to specific categories. This N value and correlation between high level features and categories is how the algorithm is trained to identify classes of images [43].

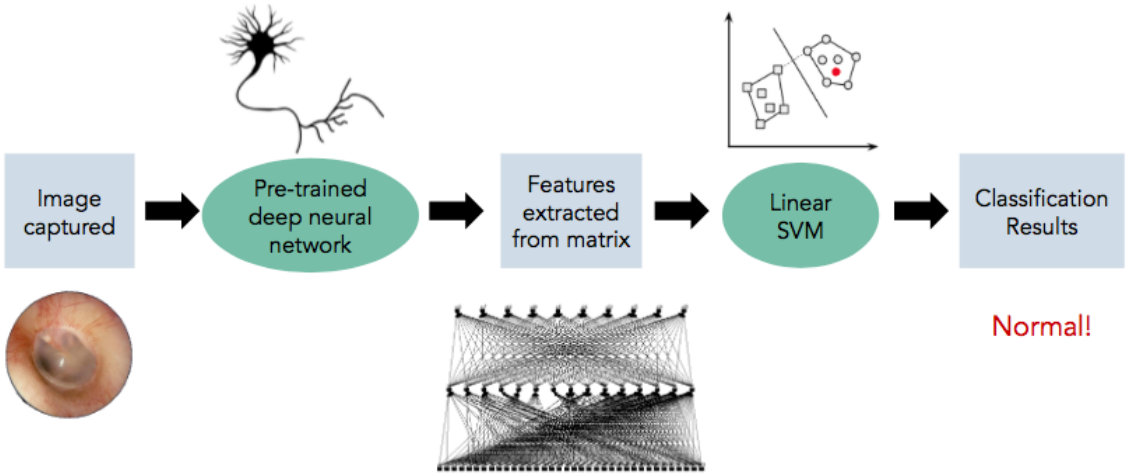


Figure 34. A schematic of how the algorithm incorporated into Auri processes a captured image to produce classification results

Verification

We verified that Auri could perform the tasks in our design blocks by testing the accuracy of the algorithm and functionality of the camera and notification mechanism.

Algorithm Testing

We ran in silico testing in Python using cross validation to understand the performance of the algorithm alone. This was our main form of testing as it allows us to test the accuracy and precision of our device without taking images of bulging and non-bulging patients ourselves.

Figure 36 shows the confusion matrix which presents information on the number of true positives, false positives, true negatives, and false negatives. Using these numbers, we could calculate the accuracy, precision, recall and other metrics of the algorithm performance. The accuracy of our classification algorithm is 92.9%. The average precision and average recall is 94% and 93%, respectively, which are well above the target specifications.

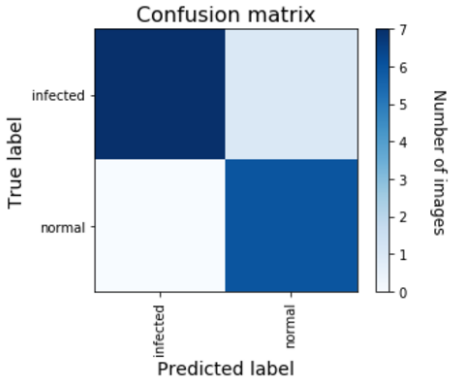


Figure 35. Confusion from the algorithm testing of the final prototype.

Prototype Testing

Our physical prototype consisted of three parts all powered and controlled by the Raspberry Pi. The first is the lighting system that consists of three bright white LEDs that are placed behind windows next to our camera demonstrated in Figure 36 and 37. Second is the camera system which uses the Raspberry Pi Spy Cam held in place by a 3D printed tip. Its functionality is demonstrated along with the lighting system in Figure 37. Lastly we have our simple red and green LED indicators to inform the pediatrician shown in Figure 38.

Figure 36. Images showing the lighting system for the spy camera. The left shows when the lighting system is off, while the right shows when the lighting system is on.

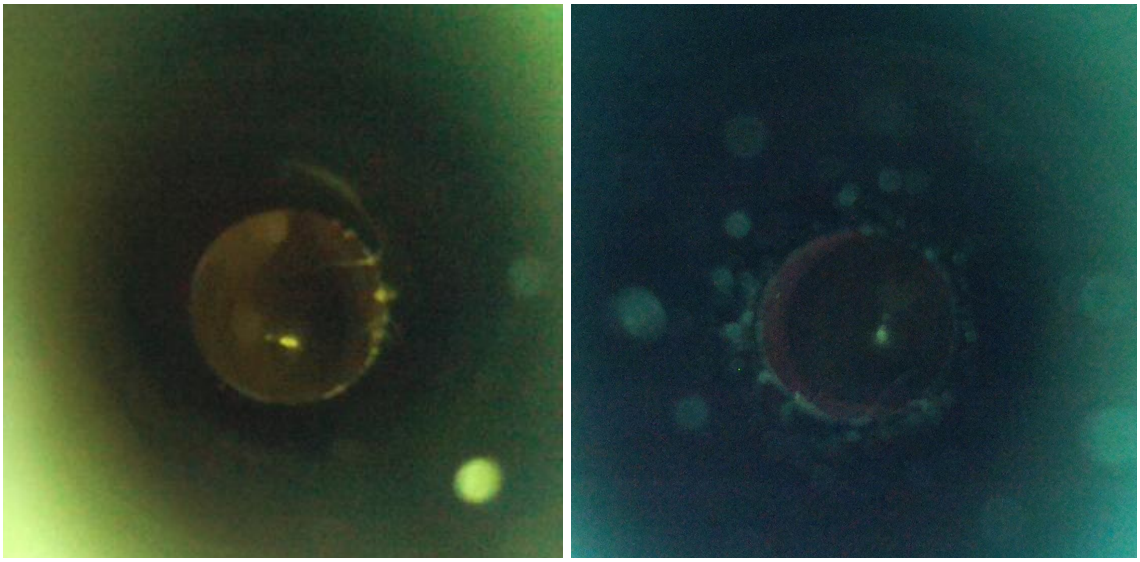


Figure 37. Sample images taken by AURI.

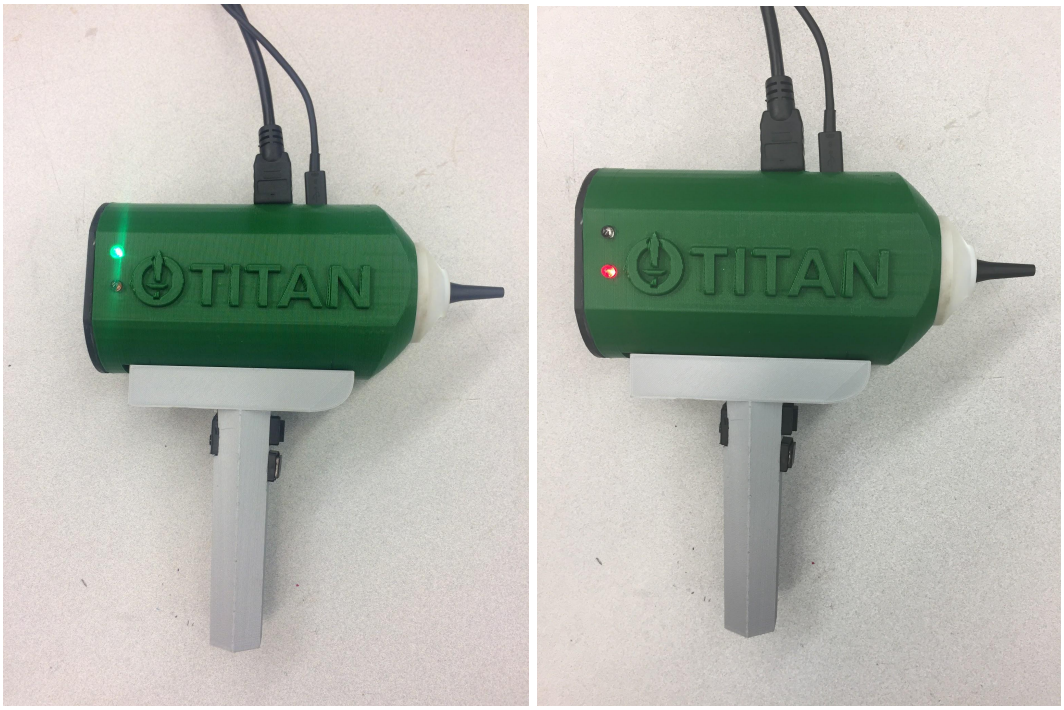


Figure 38. LED that indicates the results of the classification algorithm. The left shows the green LED, implying a normal eardrum. The rights shows the red LED, implying there is eardrum bulging as a result of a bacterial AOM.

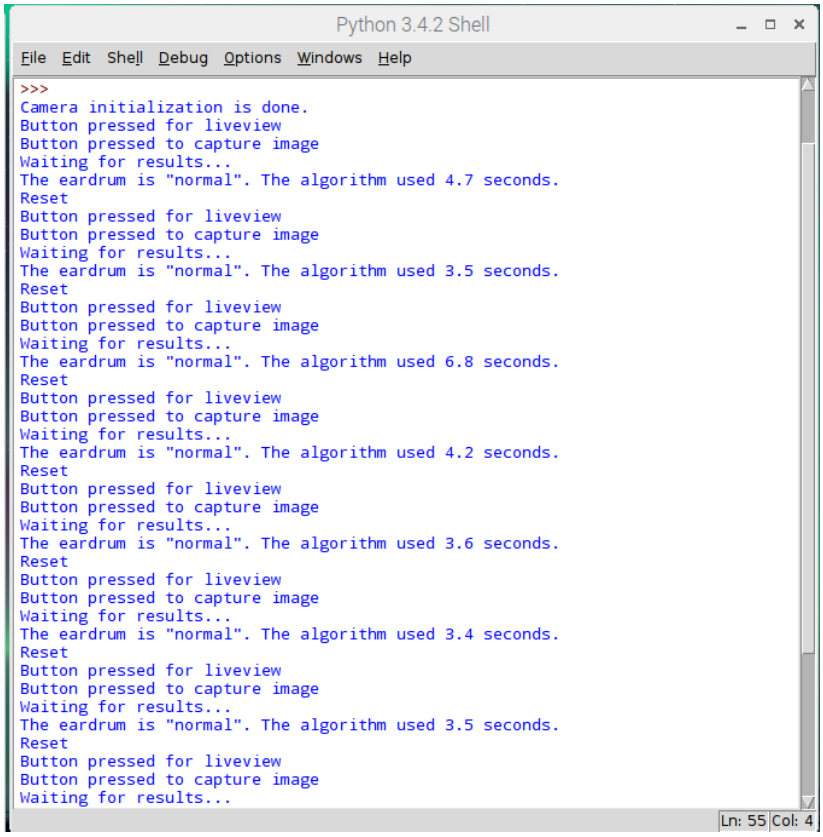


Figure 39. Screenshot of Python console showing prototype commands from using the buttons and displaying the results obtained for the image captured.

Based on these tests we can say that we are able to successfully determine if an ear infection is bacterial based on bulging, and inform the pediatrician of the diagnosis.

Validation

There are two major questions about the prototype that need to be answered with testing:

1. How accurately can we detect eardrum bulging using a handheld device with a standard disposable tip?
2. How fast does the diagnosis procedure take?

To answer the first question, we needed to understand the performance (ie. accuracy/precision/recall) and the impact of user error (variance of angle). This test requires using the prototype on two population groups, one with ear infections and one without. The group members served as the normal (ie. without ear infection) samples. We used our prototype to take the images of our eardrums while randomly adjusted the angle of the device. Given that we don't have IBR permissions to test on infected individuals we could only test the algorithm's ability to detect bulging, but not the overall device. The plan to test our prototype with infected images is outlined in conclusions and future plans. The testing results is shown in table 4 and table 5. The accuracy of AURI's algorithm is much higher compared to that of residents and

ENT doctors (table 4). The performance of the AURI algorithm is above the targeted specifications (table 5).

Table 4. Comparing the accuracy of AURI algorithm to medical residents and END doctors.

	Medical Residents	**ENT Doctors**	**AURI Algorithm**
Accuracy	61%	77%	99%

Table 5. Comparing the performance of AURI algorithm to the targeted specifications.

	Targeted Specifications	**AURI Algorithm**
Accuracy	> 85%	99%
Sensitivity	> 85%	86%
Specificity	> 95%	99%
Precision	> 85%	99%
Negative Predictive Value	> 85%	99%

To answer the second question, we needed to measure the speed of the process of acquiring an image and obtaining a diagnosis using our prototype, we used a timer to measure the amount of time it took from pressing the capture button to obtaining a diagnosis result. We did not account for the time it takes to locate the ear membrane because this is something that will be consistent with the current cycle of care that uses an otoscope. On average of 95 trials, the device took about 3.7+/-0.4 seconds to produce results. This means the algorithm does not add time into the cycle of care because we take away the time they use to make a decision visually and add only 4 seconds.

IP/Prior Art Search

A patent request for a handheld device to identify microbiological constituents of the middle ear was filed on July 10, 2014 by Stephen A. Bopart and Ryan L. Shelton from the University of Illinois [32]. Its aim is to gain approval for the examination of the middle ear using Raman spectroscopy. Raman light scattering aims to give insight into the microbiological origins of an ear infection. This is similar to our device in the goal of determining if an ear infection is bacterial and help lessen the overprescription of antibiotics. Our device aims to be superior in comfort for the patient and time spent in the doctor's office. The Raman signal has to be close to the eardrum with an optical fiber which may be uncomfortable for the child, and the accuracy of Raman in my experience depends heavily on the amount of time collecting the scattered signal because Raman is such a small portion.

A patent request for an apparatus and method of mobile imaging and analysis was submitted on September 5th of 2014 [33]. Its goal is to assist inexperienced pediatricians with imaging

analysis by making it a guided process where the device chooses the angle and position to take the images from. Its overall aim is to help the physician get a better view of the eardrum bulging and redness. Our device is superior because it will give a quantitative measurement of the eardrum bulging instead of assisting the doctor in finding a better view.

Regulatory & Reimbursement

This section will outline how we plan to attain regulatory approval and also explain our reimbursement plan for our device. OTITAN plans to pursue approval from the Food & Drug Administration because our team would like to launch our device in the U.S. market first before expanding internationally. According to the guidelines of the Food Drug & Administration, our product is a medical device because it is an instrument that will diagnose bacterial ear infections without causing any chemical actions in the body.

Our product will follow similar regulatory classification as the otoscope since they are viewed as having similar functions and risks. The otoscope is classified into device Class I, because our device is non-invasive has a very low risk and consequently low regulatory controls. However, our device will have some additional risks due to the addition of the circuit and imaging modalities that add some more electrical components. With that said, our device will be classified into Class I because the additional risks are not sufficient enough to be classified into Class II.

There are three pathways that OTITAN can choose from: 510(k), Premarket Approval, or Exemption. We believe the best course of action is to take the first track and conduct it should be feasible to acquire 510(k) approval through the FDA due to the existence of our predicates listed above, since most Class I devices follow this route. For example, the otoscope, the current device used for ear infection diagnosis, also follows the 510(k) regulatory pathway, a premarket submission that shows that the device is safe and effective.

One of our team's greatest concerns is investing in the cost for an FDA approval, given this regulatory pathway. As of 2014, it costed $31 million to bring a medical device onto the market under the 510(k) pathway, which is a large investment that OTITAN would need to get funding for. Additionally, the 510(k) pathway has a filing fee of $5,018, which would be our primary focus.

We believe that payers will be either private or public, depending on the patient. If public, the reimbursement will come from Medicaid, since the device will be used on children who may possibly come from low income families. The rest of the payers will be private, which will most likely consist of Health Maintenance Organization (HMOs). An ear infection visit should usually be covered by a small co-pay at the office, which will now increase in value, due to the addition of our more advanced device. A child will go to their usual family pediatrician, who is most likely already be in the HMO network. Ear infection visits currently cost $59 for walk-in clinics and $175 for the pediatrician's office. We infer that there will be an increase in cost, which is still to be determined, based on the cost to produce each unit.

The cycle of reimbursement should be very similar to that of a regular ear infection visit and the pediatrician's office, but with some additional costs due to the technologies in the device, which will be reflected in the International Classification of Disease (ICD) codes filed to each claim. However, some fees in the visits will most likely already be covered, depending on the insurer used. The team still needs to discuss how and where the increase in price will play as a factor in the cycle and how that will affect both the payers as well as the patients.

One important stage of the cycle of reimbursement is where the physician submits claims with the corresponding International Classification of Disease (ICD) codes. Our products may have some challenges in this team since it is uncertain what ICD codes will be used, based on the similarity of the device to what the current procedure is. For example, tympanometry, the one part of the diagnostic examination for ear infection, already has its own ICD code; however, since our device will be using new technologies to replace tympanometry, the ICD codes that need to be billed will also be replaced. The current ICD code for otitis media defines otitis media with purulent effusion as a synonym, which is the additional category that bacterial ear infections will fall under. Therefore, the ICD code for diagnosing ear infections will not change, however there may be some ICD codes added due to the new procedures that the physicians will take when they use the actual device. This will depend on the technologies used in the device, which still needs to be finalized, consequently adding to the costs that are going to be billed.

Due to this anticipated increase in costs, our team needs to consider how to increase the incentive of the payers to use our product by proving to the payers that this new device is more accurate and effective than what is already being used, which could potentially affect the ICD codes billed, and consequently the fees associated with certain ICD codes. Contrarily, the device may be deemed similar enough to the current method of otoscopic evaluation and tympanometry, where there may not be a change in codes and billing.

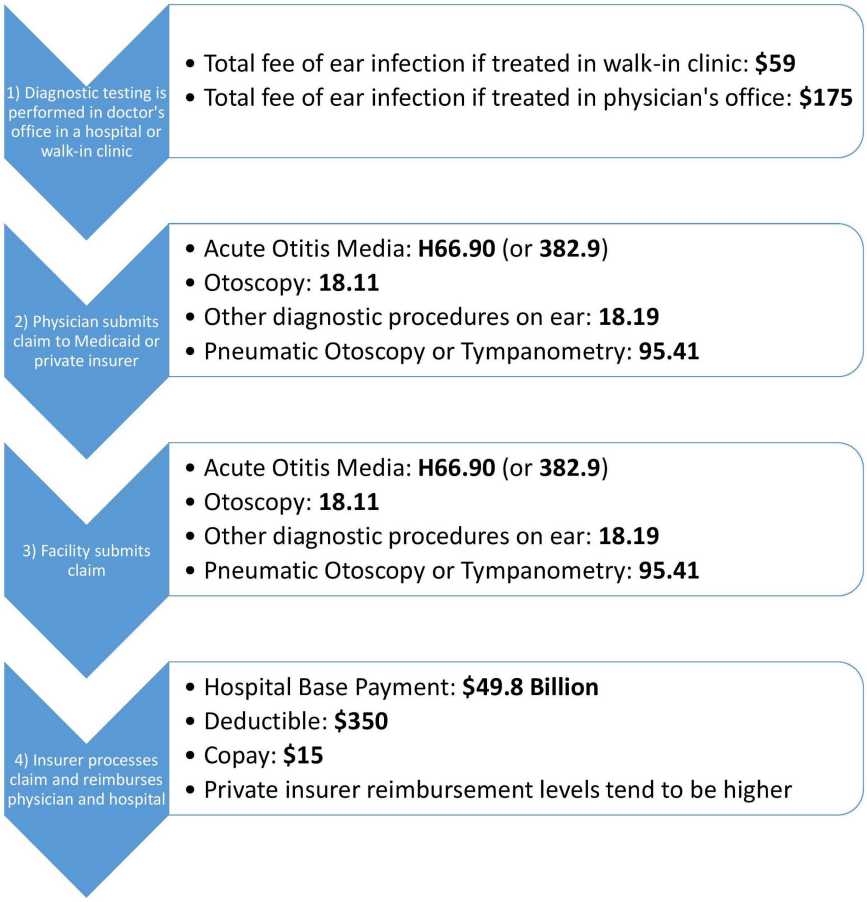


Figure 39. The Cycle of Reimbursement for office visits for diagnosing ear infections using the OTITAN device. The CPT codes come from the ICD-9-CM 2016/2017 code list and the 2016 Medicaid Fee Schedule was used to get insurance reimbursement values [17].

Three scenarios are explained below: 1) If the procedure is similar enough to the current procedure, it will be “cross-walked” to an existing ICD code and an associated low payment, even though Bi offers vast improvements on the comparative technology (e.g. increased accuracy). Reimbursement is fixed based on historic prices for the cross-walked code, so there is no reward for innovation. This scenario results in predictable payment outcome, but low incentive for investment in innovation. 2) However, if the new procedure is technically similar to the current procedure and has a completely different method, but instead is proven to provide faster and more accurate results, it will be rewarded based on the legacy fee for the existing ICD code, regardless of the costs that may be saved. The current procedure will still most likely attracts a reimbursement that is relatively high compared to some other tests 3) If the procedure is just an improved version of the current procedure, it is likely to be the test of choice in clinical setting. The cross-walked code attracts a high fee schedule compared to the low costs of investment faced for the new procedure. This scenario is more likely to be invested in since the procedure is already being used.

In order to justify reimbursement, our team needs to continue to evaluate a few things 1) how similar our device is to current methods, why payers would want to implement our device, how these similarities will affect costs, and consequently whether our device will be covered by Medicaid and private insurers and design strategies, to prove that it should be otherwise.

Ethical Considerations

Regarding the Problem

With regards to the problem of better diagnosing bacterial AOM, one main ethical concern is regarding the population mostly affected by this infection -- children. Bacterial AOM is predominantly found in children, this create an issue in properly conducting research on a vulnerable population. Research needs to be conducted for the purpose of collecting and analysing data from which generalisable conclusions may be drawn that may aid the development of the device. These ethical concerns have been translated into a complex regulatory apparatus, containing matters as participant safety, informed consent, and confidentiality [39]. Parents often receive compensation for their children's participation in research. This leads to concerns that the payments received may be coercive and lead them to participate in trials which are not in their child's best interest [40]. Additionally, while children might be the ones affected by the proper diagnosis of bacterial AOM, they are unable to make their own medical choices and determine their own method of treatment, so the decision on how to address the bacterial AOM falls on the parent or guardian and medical professional.

In our case, research would need to be conducted on children in order to determine whether or not our medical solution properly diagnoses bacterial AOM. This may include culturing the middle fluid to examine the presences of bacteria and correlating the bacteria concentration to the level of eardrum bulging. Parental permission would be necessary to obtain and test the middle ear fluid. In order to obtain parent consent, there needs to be a reassurance for parents that a clinical trial is necessary and beneficial to their children. Children are a necessary group for clinical trials as their distinct developmental and physiological differences are part of the reason why they are more susceptible to AOM. In conducting research, there still needs to be consideration for adequate and appropriate treatment. Prolonging the cycle of care for any reason during clinical trials would be problematic for children as it increases symptoms, pain, and also the likelihood of hearing loss.

Due to the complexity relating to children, there aren’t many pediatric medical device that have been brought to market and many have not yet approved. CelloScope is a clip-on attachment to a smartphone, which allows remote diagnosis of otitis media. It bypasses the clinical trial phase by being a diagnostic tool that only provides a picture of the eardrum. Therefore, the diagnosis decision relies on the medical professionals. CelloScope is a Class 1 device exempts it from FDA approval or clearance to the low-risk level associated with this type of device [41]. Abriiz is a web-based app that engages children, parents and doctors to manage chronic condition. It is considered a medical device by the FDA, but the app is not subject to additional regulatory requirements at this point, given that it is a tool that integrates and keeps track of data from other FDA-regulated medical devices, such as blood glucose monitors [42].

Currently, the ICTRP is a committee that focuses on promoting ethical and clinical trials for children. The ICTRP sets specific ethical and clinical considerations into account for the designing and evaluating of the clinical trials. Additionally, the FDA Human Subject Protection (HSP)/Bioresearch Monitoring Initiative (BIMO) are meant to address oversights currently present in clinical trials and in data integrity [38]. The HSP/BIMO handles clinical trials of FDA-regulated products, including medical devices with the goal of protecting the rights, safety, and welfare of the clinical trial subjects. For work involving children, an additional safeguard regulation was added to clinical investigations. The FDA in cooperation with the Children's Health Act, requires that all research involving children is conducted, supported, or regulated by the Department of Health and Human Services (HHS). This regulation provides additional protection for children and was added due to an increase in child enrollment for clinical investigations due to ongoing pediatric initiatives.

Regarding the Solution

In many digital health data fields, it is a common strategy to send various digitalized medical data to the local server and apply algorithms to extract meaningful information for interpretation. Our product follows similar path and it needs to collect information -- like information regarding the eardrum, age, and etc. -- for the prediction of bacterial ear infection. Similar to hospitals, such analysis asks for patients to create personal health record in the local server, which raises concerns regarding data privacy.

Health professionals who have access to the data can inappropriately disclosed such information, whether it is inadvertent or not. Improper handling of information can include disclosure of information to friends or colleague unintentionally. Furthermore, when medical records are stored in the local server, it increases the vulnerability of privacy in various ways. Cyber attackers can utilize multiple information sources (like social networks and public records) to reconstruct comprehensive user profiles, with various highly sensitive and private information. If the attackers are equipped with information retrieval and data mining techniques, patients could be easily exposed. On the other note, skillful hackers may have direct access to patients' private information after hacking into the data storing system.

The group directly affected by diagnosis through data analysis will be the patients; and a large proportion of those patients will be children. The children is unlikely to be concerned with their personal information at this age, but their parents will be concerned because their are usually the guardian of their children, which means their personal information is often included in the record.

BioSec is a company produces implantable medical devices. It uses efficient methods for securely communicating with medical sensors by using physiological values as cryptographic keys [32]. Todd Coleman and his colleagues come up with a wearable device that monitor the fetus' heart rate. The data analysis circuit is integrated into the device to provide patient's information with less exposure to the web [33]. Another category of medical devices that deal

with privacy concerns are fitness tracker devices such as fitbit and apple watch. Apple implement powerful safeguards into their operating systems.

To address the privacy concern: firstly, we will separate patient's personal information (such as age) from the information that is essential to the prediction of bacterial infection (such as eardrum image). The local server will only store those disease-related information for data analysis. Thereby, giving a smaller target for the attackers. In addition, we will limit health professional's access to patient's personal data, allowing the patient have an extra control over their privacy. That is to say, health professionals should only be able to see the disease-related information. Lastly, we would strictly follow the The Health Insurance Portability and Accountability Act (HIPAA) guidelines to protect our customer's personal information. Privacy and Security Rules under HIPAA are designed to protect sensitive information known as Protected Health Information (PHI) [30]. The Health Information Technology for Economic and Clinical Health Act of 2009 expanded HIPAA's coverage to include electronic information and require notification of breaches [30].

Conclusion and Future Works

Auri is a rapid and painless method to accurately diagnose bacterial ear infection from analysis of eardrum bulging. Our algorithm was very successful at classifying bulging thanks to the from TensorFlow. The overall device has been successful in identifying normal eardrum from among our group. Based on these tests, we have found Auri to be a successful prototype, but there is room for more improvements and testing once permissions are acquired.

The envisioned prototype needs to run the algorithm on a smaller controller/processor that will allow us to use a smaller camera and miniaturize the device overall. To achieve this, we need to make several improvements for the current prototype

1. Increase the database (image library) to obtain a higher accuracy for the classification algorithm
2. Shift the prototype's controller/processor from the raspberry pi to a processor
3. Design a smaller camera similar to the ento camera size to fit into the disposable tip, and have a better range of focus.
4. Miniaturize the overall design of the device to increase ease of use

To increase the size of our database we plan on partnering with pediatricians and ENT experts who may send us images that they have acquired if we let them use our device for free. We also plan to partner with ENT's who perform myringotomy in order to add more images of confirmed bacterial ear infections to the database.

Moving away from the Raspberry Pi will help with the limit to device size as well as camera size. Reducing device size will increase the comfort and usability for the pediatrician, and a smaller camera size will improve image quality to better emphasize physical features for the algorithm to identify.

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