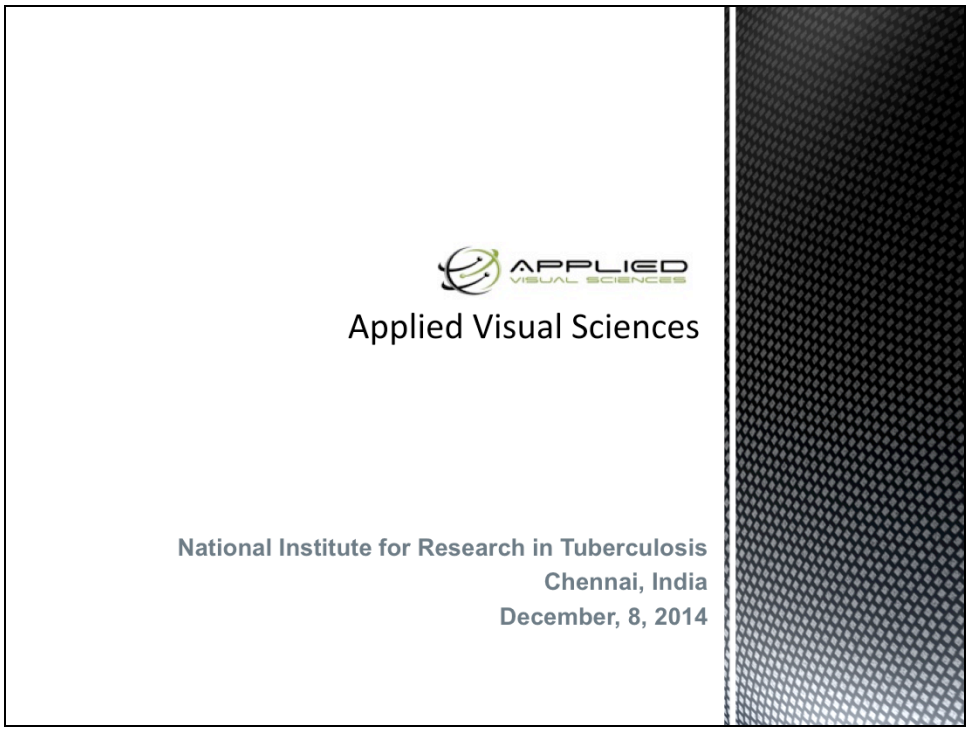
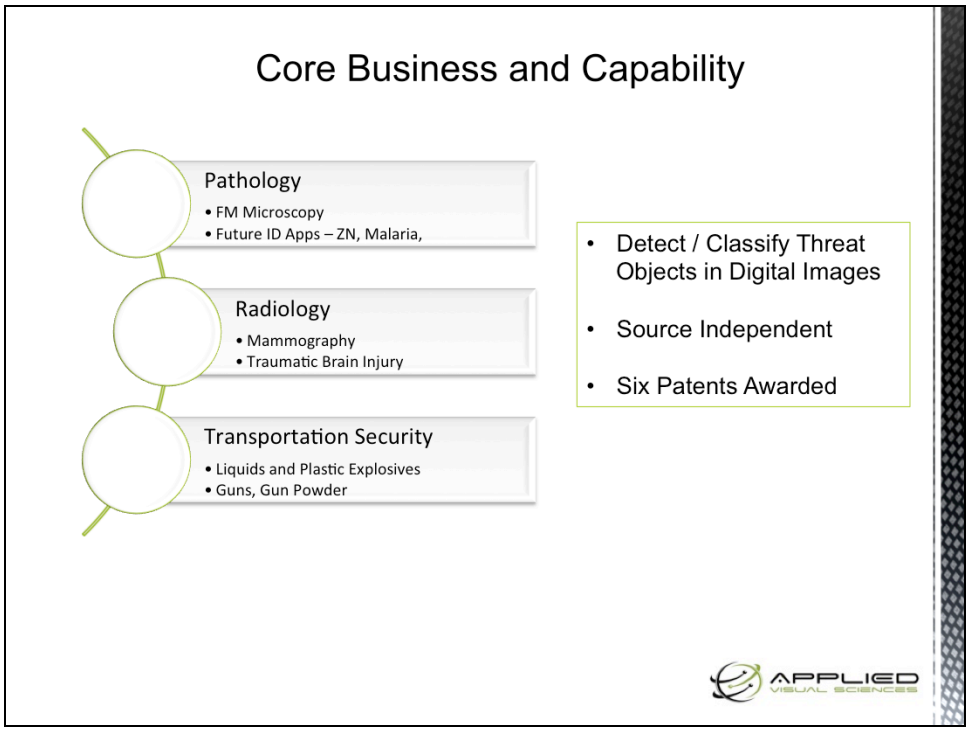
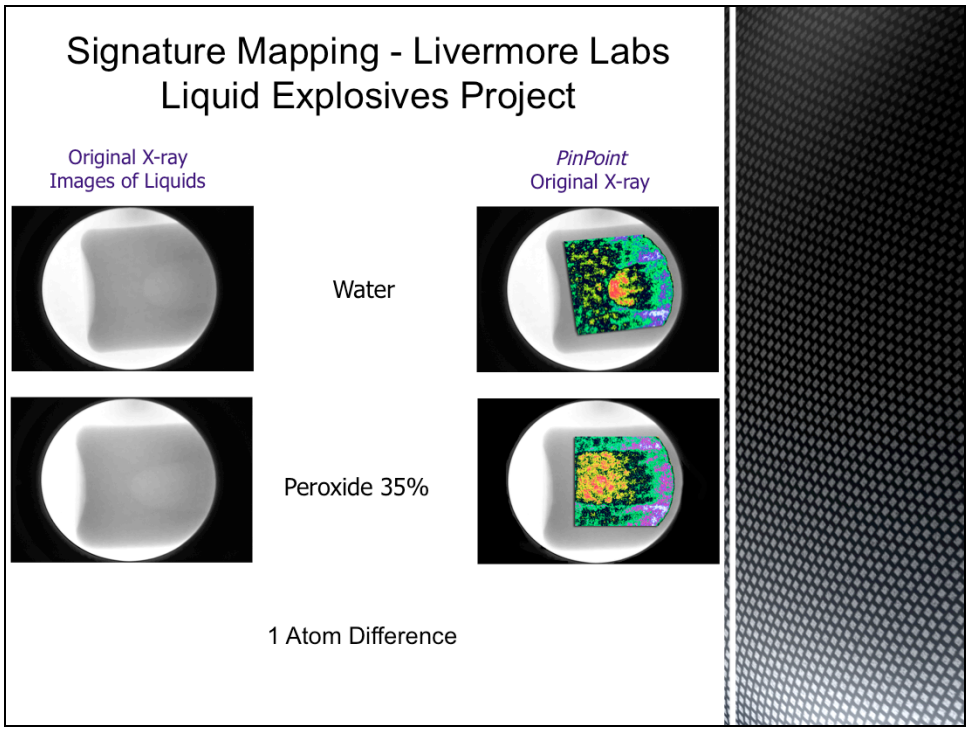


Applied Visual Sciences in a software development company. We integrate and leverage existing diagnostic technologies by adding computer vision software algorithms that are intended to improve the diagnostic performance.

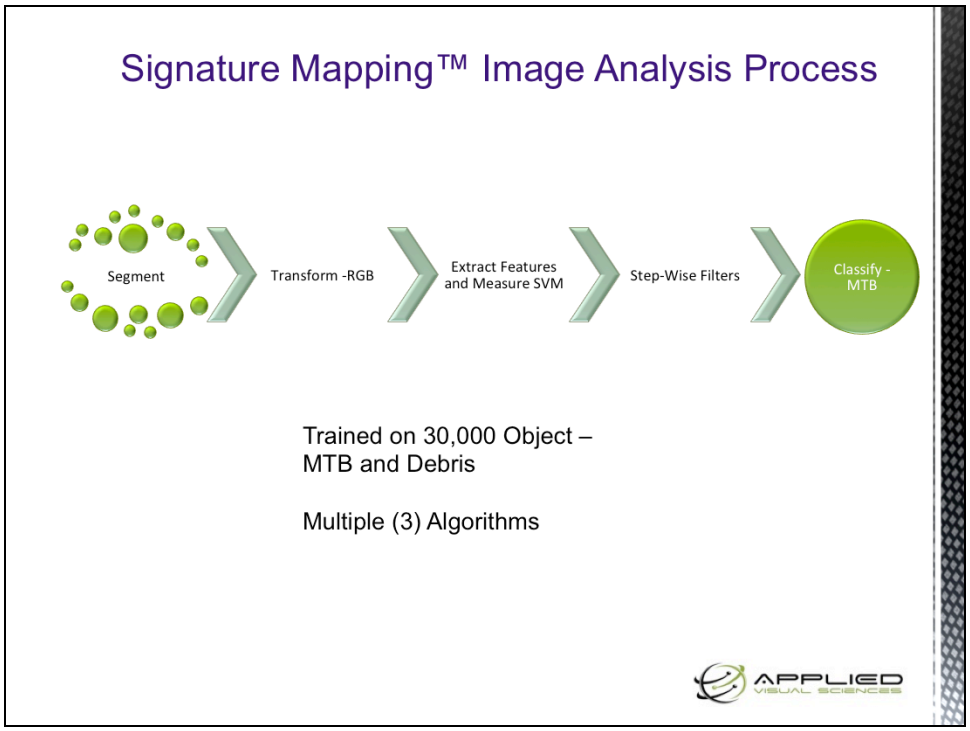


The company trains software using 6 patented image analysis methods. This training is intended to detect threat objects in digital images. These threats may be a liquid explosive in carry-on plane luggage. It could be cancer found in a mammogram, or it could be MTB in a digital image taken of a sputum smear taken by a camera mounted to a microscope. It does not matter if the source of the image is an X-ray, MRI, Ultrasound, Infrared, or any other source. The methods work on any digital image.



Human vision has limitations. It can be claimed that human vision will never be able to outperform machine or computer vision in identifying specific threats in digital images.

Perhaps one of the best examples of this limitation is to look at an X-ray of water and hydrogen peroxide. On the left is an X-ray image taken of both liquids. Each was scanned by the same scanner at the airport. The human reviewing this images will never be able to tell the differences between the two, which happens to be just 1 atom (H_2O vs. H_2O_2). This is one reason why you can not take liquids through an airport security station. However, if you look at the images on the right, the software has been able to be trained to differentiate the two sufficiently to be able to "see" the difference. In this example the hydrogen peroxide atom is below a 35% concentration, which makes it a liquid explosive.



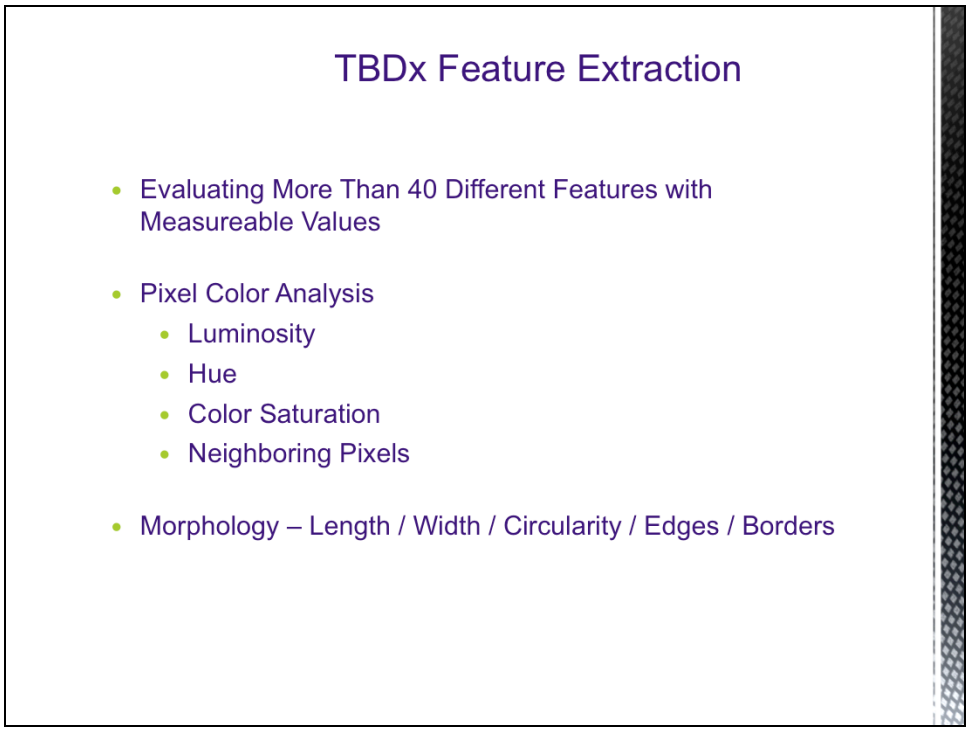
This slide illustrates the general path taken for image analysis.

- The most important is at the very beginning where the system identifies ALL of the likely threat objects of interest. At this point the segmentation needs to be in the high 90's percentiles as each other step tends to filter out the objects as it goes through the path.

- The second stage will convert the object into 3 channels of color, Red-Blue-Green. These channels are manipulated by various transforms and each transform can be used for subsequent transforms. The purpose is to begin to understand which of the channels most helps to begin differentiating threats from non-threats.

- From this stage the analysis path will begin to extract various features that are measureable and helpful in further distinguishing the object. These measurements are further filtered through a support-vector machine we have built, and at the end additional thresholds are applied in a step-wise classification process.

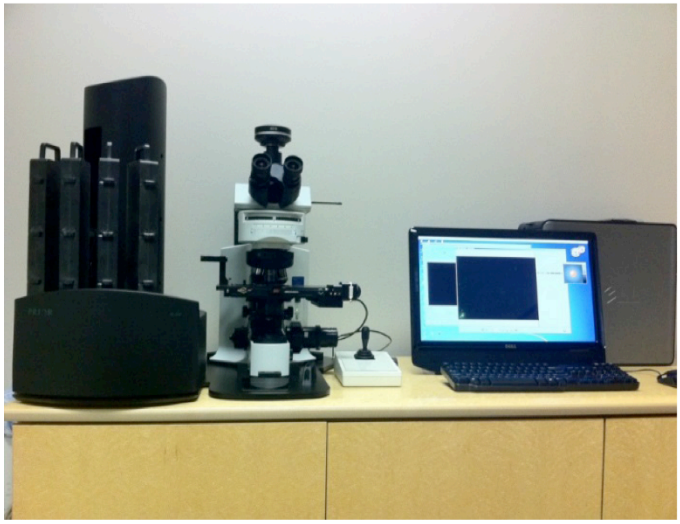
- This leads to a classification of the object being MTB or debris.



We evaluate more than 40 features for determining whether an object is an MTB or not.

We analyze pixels and their luminosity, color saturation, hue, texture, and how there neighborhood (or nearby) pixels appear. We look at shape…width, length, borders, edges, circularity, and more. All of these measurements helps us to find correlating measurements to determine what is TB or not.

TBDx Platform – Autoloader Configuration

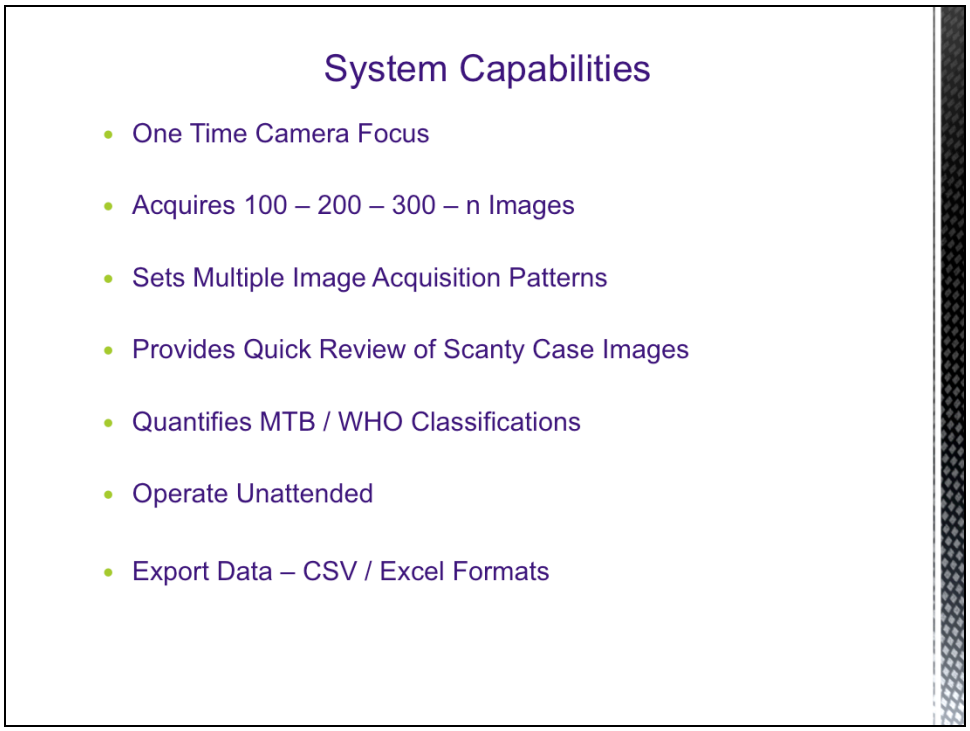


This is a picture of TBDx, configured for high volume settings. A second configuration does not include the slide loader and can process 4 slides automatically.

- On the left is a Prior Scientific automated slide loader. Each of the four cassettes holds 50 slides. The operator can run 1 or 4 cassettes. The slide loader has a slide reader that inventories each slot in the cassette for the presence of a slide. The arm lifts the slide on to the automated slide stage. It has a bar code reader on the arm so the patient ID can be automatically entered into the TBDx software application.
- The autoloader is attached to an Olympus BX-41 microscope that is equipped with an Olympus XC-10 camera. The system automatically focuses the camera and begins to acquire images. The user can set the software to capture 100-300-n images.
- The workstation operates user controllable software that operates the equipment, and the images are stored in a database where they are analyzed for the presence of MTB objects. A report is automatically generated.

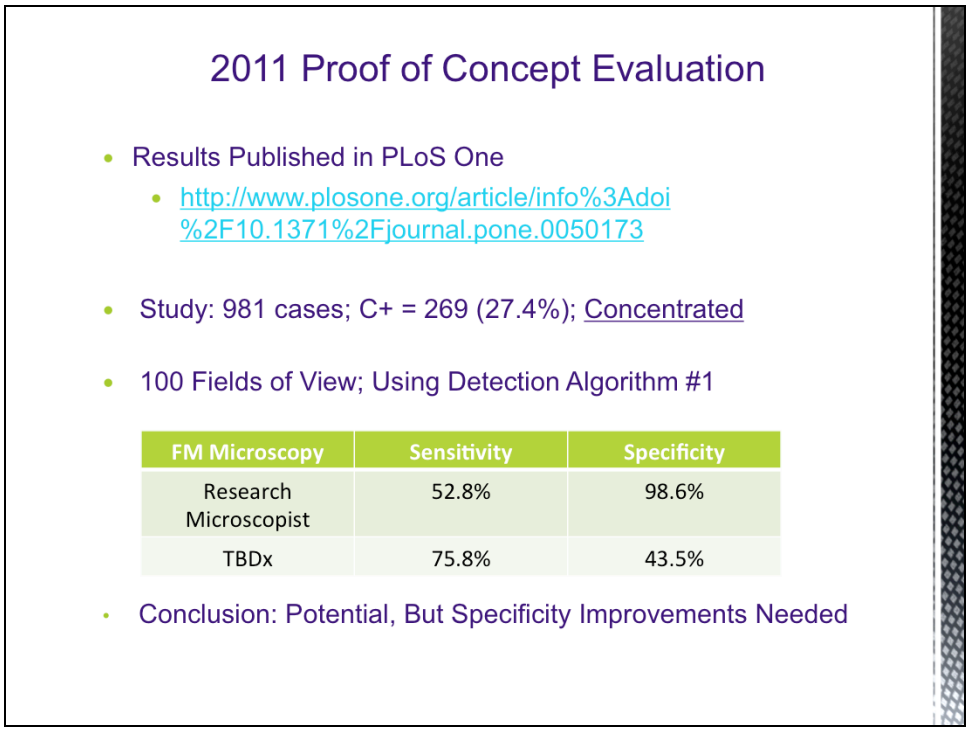
TBDx Platform – Autoloader Configuration

This is a picture of the setup during the evaluation of the technology in Abuja, Nigeria. The autoloader slide cassettes have been removed.



- The camera focuses just one time, rather than focusing each time an image is to be taken. This enables pictures to be taken and processed quickly and accurately.
- Though the user can acquire any number of images, all of the evaluations so far have been based on acquiring 300 images. The represents a sample area that is about 50% of what the human eye sees when evaluating a smear and looking at 100 fields of view.
- Multiple acquisition patterns can be set, though the evaluations so far have had either 3 different patterns of 100 images each pattern, or just one pattern of 300 images.
- The software has a "quick review" application or feature that permits the microscopist to review the images in those cases that the software has assessed as "scanty". This is a feature that can be used but is not a requirement.
- Each MTB object is counted and the precise number of objects is noted in the report along with a WHO grading classification.
- The system can be operated unattended. Once it is launched, the system operated in a fully operational mode.
- The data base can be exported and the system can be integrated with any Laboratory Information System (LIS).

- We have completed three independent evaluations.
- Two have taken place at the National Reference Laboratory in Johannesburg, in 2011 and 2013.
- Recently the National Reference Lab in Abuja, Nigeria completed their evaluation of TBDx.
- Two evaluations are either underway or planned, under the direction of the Foundation for Innovative New Diagnostics (FIND). One began in the Fall of 2014 in Lima, Peru, and the second will begin in January, 2015 in Ho Chi Minh City, Vietnam.



- The first evaluation was a Proof of Concept intended to assess the feasibility that software would be able to automatically and consistently detect MTB in digital images. The test included culture as the reference standard, and the objective was to measure the performance of a microscopist and TBDx. The microscopist had 40 years of microscopy experience.
- The system evaluated rather old slides from a previous study. All smears were concentrated. At the time the TBDx software operated using Algorithm #1 which was highly sensitive.
- The results showed that in spite of the age of the slides, the software could be more sensitive than a very seasoned microscopist.
- However, the specificity was unacceptable. The team conducting the study, published in PLoS One, agreed that the software and the equipment configuration had potential, but additional work was needed in training the software to remove false positives and improve specificity.

2013 NRL Evaluation

- Results Presented at Late Breaker Session of the 44th Union World Conference in Paris by Nazir Ismail
- Study Objectives
  1. Evaluate New Detection Improvements
     - Research Microscopist vs. TBDx – 300 FOV (3@100)
  2. Screening: Confirm All TBDx+ with GXP
- Study: 1009 cases; C+ = 109 (10.8%); Concentrated; Algorithm #3 (Design Goal = 80/80)
- Objective #1 – TBDx – By Itself

FM Microscopy	Sensitivity	Specificity
Research Microscopist	68.8%	99.2%
All TBDx Positives	79.8%	78.9%
TBDx (Scanty 1 = Negative)	73.4%	95.7%

- After considerable work revising the software algorithms, conducting internal tests that were facilitated from slides provided by Johns Hopkins University, the Research Institute of Japan, and the National Reference Laboratory in Johannesburg, two new and better performing algorithms were created. Additionally a series of step-wise classifiers were created to remove false positives.
- The TBDx system was re-evaluated at the NRL in South Africa. Again, all smears were concentrated. Liquid Culture was used as the gold standard. TBDx was compared with expert readings from two microscopist, each having 40 years of microscopy experience. One microscopist would read the slide, then it would be read by TBDx, then read a final time by a second microscopist.
- There were two objectives. One was to test the Sensitivity, Specificity, PPV and NPV of the new software algorithm, and the other was to see how TBDx could perform as a screening tool for GeneXpert.
- As the slide notes, the TBDx technology outperformed the sensitivity of two seasoned microscopist, however it was slightly less specific when Scatnty 1 cases are treated as negative. Improvements over the previous software algorithm showed that you could improve both sensitivity AND specificity.
- Treating the 158 Scanty 1 cases as negative led to Sensitivity declining to 73.4% but Specificity increased to 95.7%.

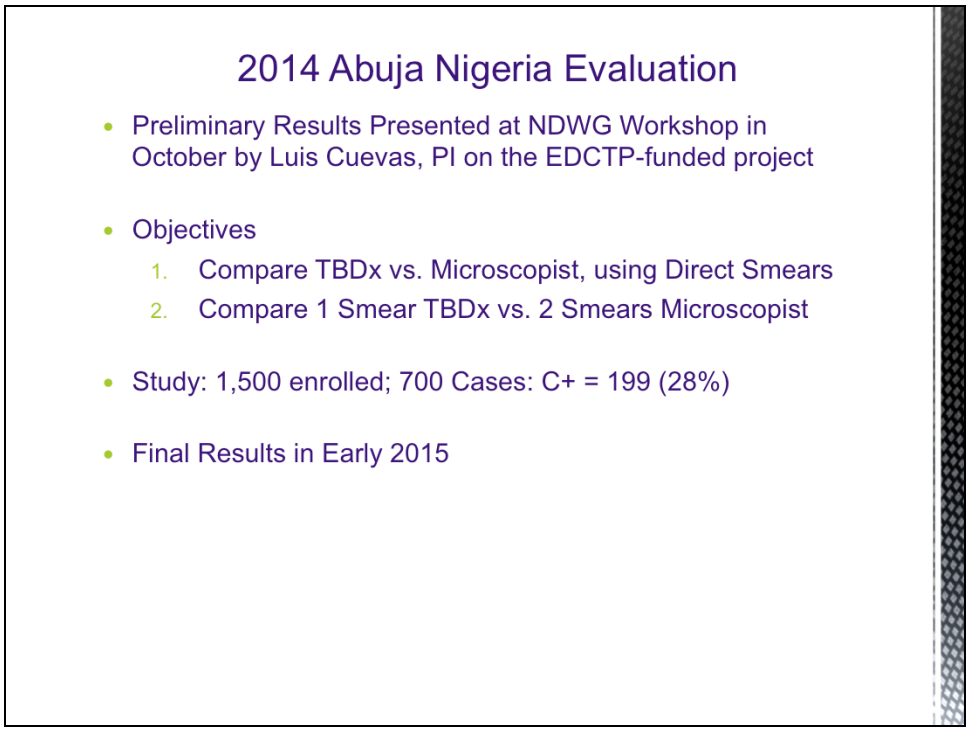
2013 NRL Evaluation

- Objective 2 – TBDx with GXP Confirmation

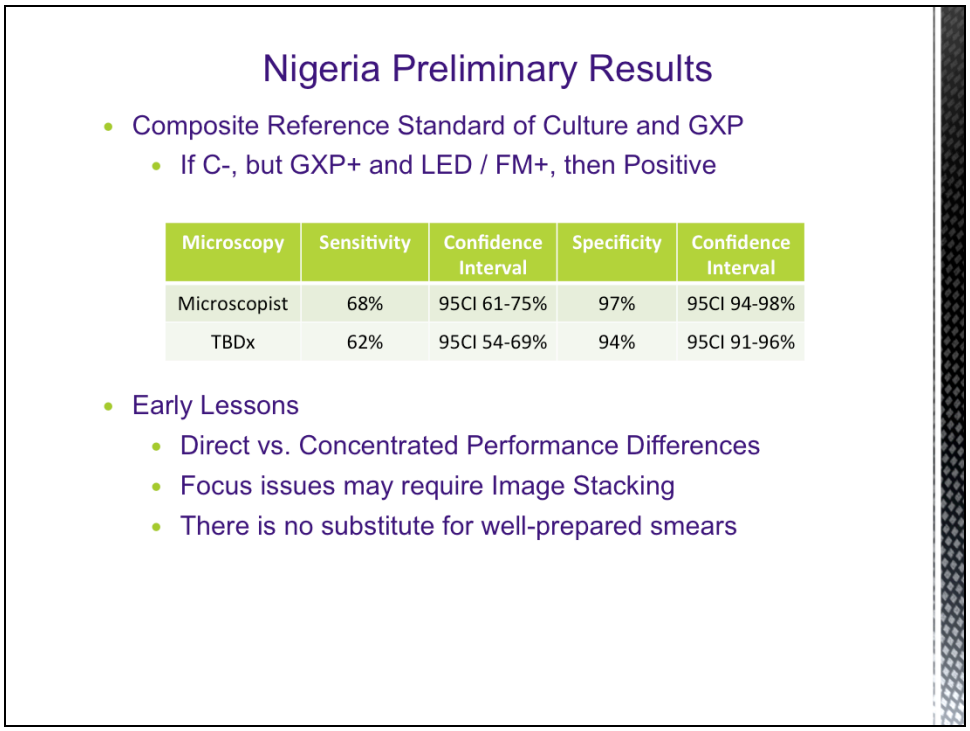
GXP Confirmations	Sensitivity	Specificity	# of GXP Tests
All TBDx Positives	77.6%	98.9%	277
Scanty 1-9	78.0%	98.8%	207
Scanty 2-9	72.9%	99.3%	49

- Conclusions
  - TBDx could be a useful screening tool to GXP
    - 78% sensitivity with 80% fewer GXP tests
    - 73% sensitivity with 90% fewer GXP tests
  - Recommend demonstration studies in different settings

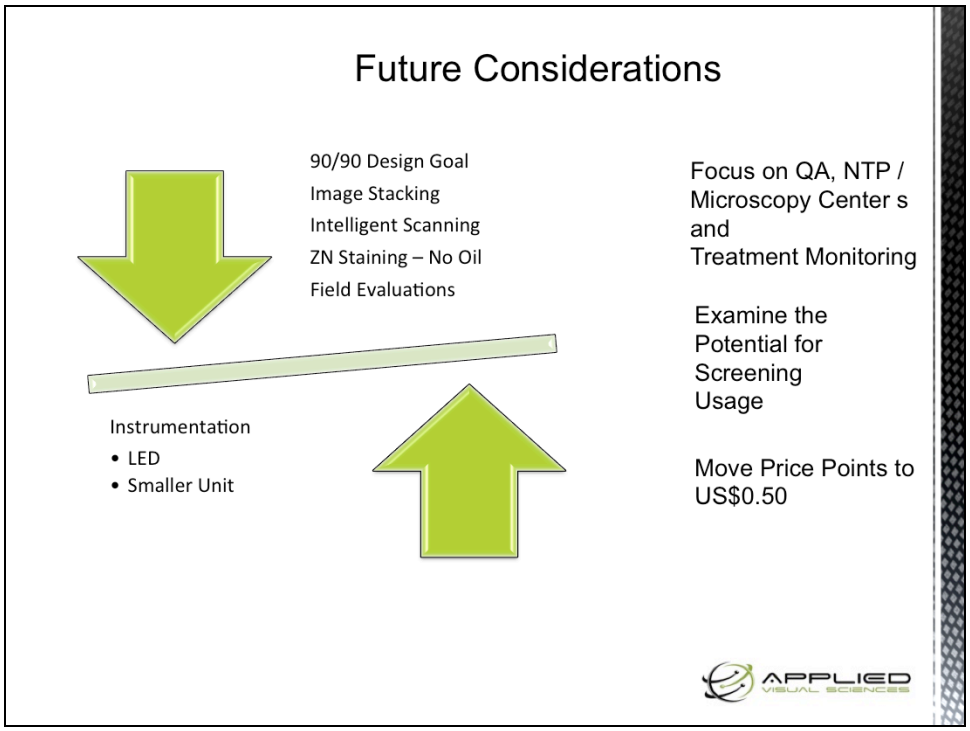
- Each TBDx positive case was confirmed by a GeneXpert test.
- The review committee assessed the performance combination of TBDx and GeneXpert where TBDx screens for GeneXpert.
- TBDx identified 277 positive cases, and if GeneXpert were to evaluate all of them, sensitivity would decline to 77.6%, but the specificity would increase to 98.9%, and it would require 277 GeneXpert tests.
- The review committee then wanted to see the performance of the combination where all TBDx classifications were accepted as correct EXCEPT Scanty cases, which would then receive a GeneXpert confirmation. Sensitivity and specificity would remain the same, but only 207 GeneXpert tests would be needed.
- The committee then wanted to see performance measurements if Scanty 1 was treated as Normal. In this case, then, only Scanty 2-9 cases would have a GeneXpert test. Sensitivity declined to 73%, Specificity increased to 99.3%, and just 49 GeneXpert tests would be needed.
- These results were presented during the Late Breaker session of the 44th Union World Conference on Lung Health in 2013. The committee has written three drafts and hopes complete the final draft in December and submit it to a medical journal in early 2015.



- The third TBDx evaluation was directed by Luis Cuevas of the Liverpool School of Tropical Medicine and was funded by the EDCTP. The test took place beginning in June, 2014.
- This test offered unique opportunities. This was the first test of the technology using direct smears. Additionally there was an interest in knowing how the technology would compare if the microscopist evaluated two slides, and TBDx evaluated just one. Both were unique opportunities to better understand operational and detection performance.
- The evaluation included a composite reference standard. Culture (LJ) was the gold standard. However, if the results were Culture Negative but GeneXpert Positive and LED / FM Positive the result was considered to be positive.



- Preliminary findings were presented to the audience attending the annual meeting of the New Diagnostic Working Group of the Stop TB Partnership, just prior to the 45th Union World Conference on Lung Health this year in Barcelona.
- The findings suggest that performance between the microscopist and TBDx are equivalent.
- Assuming that examining two smears can increase positivity by 10%, TBDx would likely before at 68% or better. The finding suggest that there could be an performance difference for TBDx when examining direct smears vs. concentrated smears.
- Typically concentrated smears produce sensitivity improvements of 10% and this suggests that TBDx would have performed in the 75% sensitivity range, which would be expected for Algorithm 3 today.
- The data suggests that some of the cases that were missed by TBDx were likely due to badly focused images that made it impossible for image analysis to properly segment the image and detect threat objects. This focus issue can be addressed by "stacking" images, taking multiple image of one position and combining them into one composite image that can be evaluated.
- All this noted, there is no substitute for a well-prepared smear. All good image analysis results begin with a well-prepared, stained slide.



As we look to the future APVS hopes to introduce multiple improvements in 2015.

- We are evaluating Algorithm #2, which is more sensitive but less specific, and we are making adjustments so that this algorithm can approach 90% sensitivity and 90% specificity.
- We intend to add image stacking to the routine whenever the technology evaluates Direct smears. This will result in a better image and that will lead to better MTB detection.
- We will be introducing “intelligent” scanning so that when the system has found a 1+, 2++, or 3+++ case the system will stop acquiring images and move along to the next case.
- We intend to develop ZN stained slide algorithms now that we can acquire images without the use of oil.
- We see the TBDx 200-slide configuration most useful in high volume settings, likely in a national and intermediate reference laboratory setting. We see that the technology could be used for EQA. It has a potential for screening and triage. However, new instrumentation are needed to take this solution to the level of primary care.
- We hope to reduce the price points down to a level where a slide can be examined by the software at US$0.50 per slide.