Written Testimony of Dr. Bryan F. Shaw Regarding the CRADLE Medical App.

Summary: 1 in 80 children will exhibit "white eye" or *leukocoria* (Fig. 1) as a symptom of a variety of eye diseases. A free medical app developed by Greg Hamerly, Ryan Henning, and myself at Baylor University can help parents and doctors detect this symptom, which can be tough to spot (Fig. 2-3). The app is known as "CRADLE" (**C**ompute**R** **A**ssisted **D**etector of **LE**ucokoria) and since its release in 2014 for the iPhone (2015 for Android), parents across the world have used this free app to save their children's vision and life, for example by quickly detecting "white eye" associated with the aggressive cancer retinoblastoma. Doctors in the U.S., Germany, and Guatemala have also taken advantage of this free technology and are now testing CRADLE in urban and remote clinical settings as an alternative (or compliment) to the ophthalmoscope. My colleagues and I are now optimizing CRADLE and testing it under different clinical settings. We know that CRADLE works, but we want to know how well it works. The largest obstacle in the initial development of CRADLE, and its ongoing optimization is receiving funding. The development of CRADLE has relied on financial support from private donors and from Baylor University.

Pediatric Eye Diseases are Widespread and Difficult to Detect. Each year in the U.S., approximately 500,000 children will develop or will be born with various disorders of the eye, including refractive error, retinoblastoma (cancer of the retina), pediatric cataract, Coats' disease, persistent fetal vasculature, amblyopia, strabismus, and myelin retinal nerve fiber layer. Catching these disorders early can prevent vision impairment and in the case of retinoblastoma, death. The cardinal symptom of these disorders will often be *leukocoria*, a white pupillary reflex that can appear in a photograph or can be observed by a doctor when shining a light into the child's eye (Fig. 1). Unfortunately, leukocoria can go unnoticed by a parent and often goes undetected by a pediatrician.

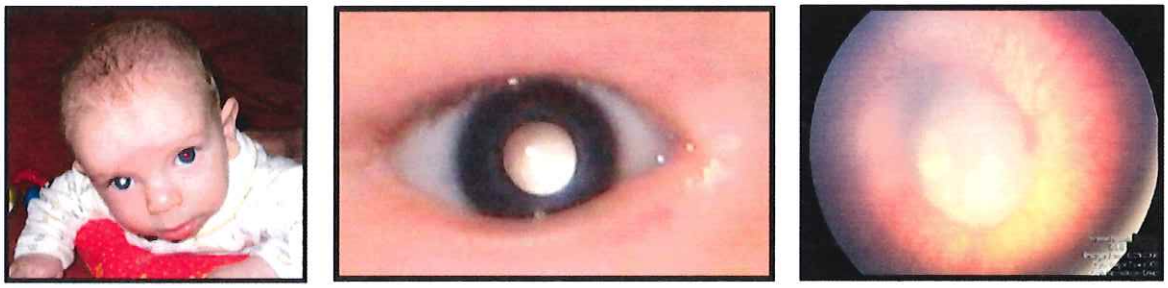

Figure 1. Left and center images: an example of leukocoria in a child with retinoblastoma (taken by mother before diagnosis). Right image: fundus photograph of the same Rb tumor from the same eye in left and center images (collected by an ophthalmologist after diagnosis). Images donated by Bryan Shaw.

My own family's experience with the challenges of screening for eye disease cost my son Noah most of his vision, nearly cost him his life, and has cost our healthcare system hundreds of thousands of dollars dealing with the results of his late diagnosis. Noah was born with aggressive retinoblastoma tumors in both of his eyes. Doctors were not the first to detect these tumors: Noah passed all of his eye examinations at 3 days, 1 week, 2 weeks, 1 month, 6 weeks, 2 months and 3 months. It was his mother's digital camera that detected his tumors at 3 months old. An ophthalmologist confirmed the diagnosis a few hours after Noah's mother informed his pediatrician about her observation of leukocoria. Noah would go

on to receive systemic chemotherapy, would lose his right eye, and would receive ~ 30 cycles of radiation treatment to his left eye.

Although Noah's mother noticed these pictures when he was 3 months old, we found later that leukocoria had been occurring in pictures since Noah was 12 days old. Noah's ophthalmologist predicted that, had we diagnosed Noah in the first month of life, only laser- and cryotherapy would have been used, without the need to remove the right eye or irradiate the left eye. Studies suggest that my family's experience (including our pediatrician's inability to detect Rb, *ab initio*) is common.

After realizing that doctors and parents need better tools to screen for leukocoria in children, my colleagues and I at Baylor University, Greg Hamerly and Ryan Henning, invented CRADLE. CRADLE has been available on Apple's App Store since October, 2014, and on Google Play since July 2015 under the name "White Eye Detector".

How CRADLE Works. CRADLE (Fig. 2) searches pictures on the smartphone's hard drive for examples of leukocoria. CRADLE can also convert the smartphone into a computer-assisted ophthalmoscope by activating the LED and video camera. In this live-video mode, CRADLE software analyzes each video frame for leukocoria (in real time), constantly tracking each eye and positioning green boxes around normal eyes that exhibit red or black pupillary reflexes, while positioning red boxes around eyes that exhibit white pupillary reflexes in one or more video frames. We have also incorporated CRADLE software into other photographic devices, including an inexpensive ($16) LED Webcam (Fig. 3).

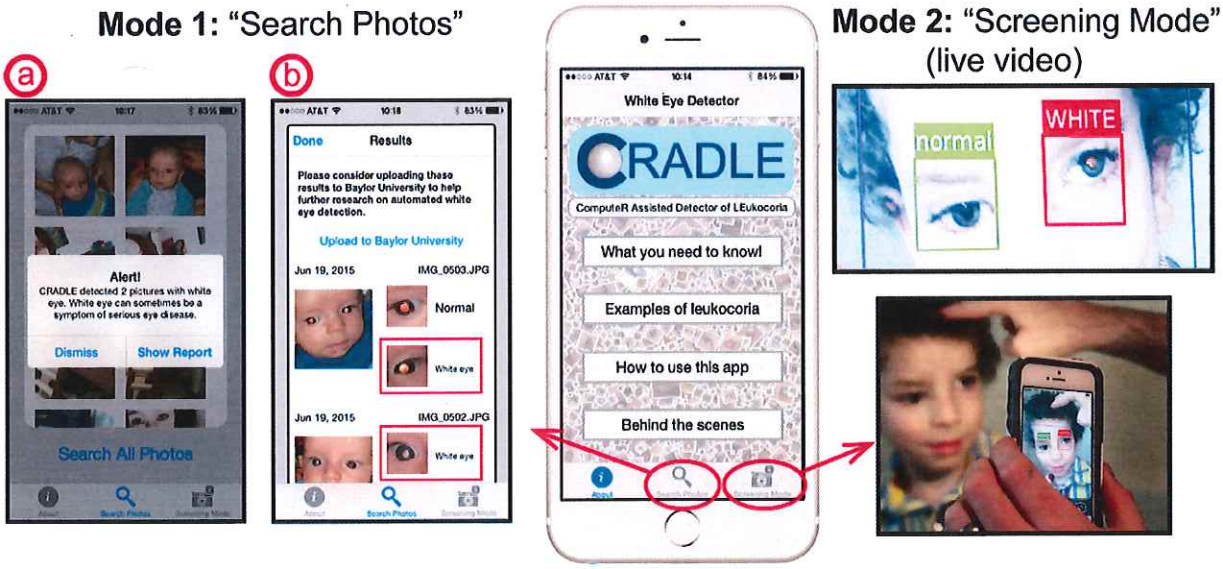

Figure 2. ComputeR Assisted Detector of LEukocoria (CRADLE). The free CRADLE smartphone/tablet app is listed in Apple's App Store and Google Play as "White Eye Detector". The app operates in two modes: "Search Photos" (Mode 1) and "Screening Mode" (Mode 2). Far left: "Search Photos" mode. CRADLE can search all images stored on the device (or single images, via "tapping") for leukocoria. Far right: "Screening Mode". In screening mode, the smartphone becomes an improvised ophthalmoscope and tracks and tests the eye in real time. Note: the user needs internet access to download CRADLE, but not to use it, i.e., CRADLE software is saved to (operates independently on) each person's smartphone. Images donated by Bryan Shaw.

CRADLE's Global Impact. In less than 18 months, and without forming any type of corporation or organization to market or promote CRADLE—we are just a group of academics who put an app on the web—CRADLE has received ~ 45,000 downloads on all continents. It is most popular in Germany, where it has received 20,000 downloads. In 2015, two families in Germany used CRADLE to detect rétinoblastoma in their children long before doctors detected the disease. Retinoblastoma is an exclusively pediatric eye cancer that affects 8,000 children each year, usually striking the developing retina before the 2nd birthday. Retinoblastoma will kill 4,000 of these children, and it will diminish the vision of survivors. In these two German children, CRADLE caught retinoblastoma at such an early stage that the children only received laser therapy, and these children were able to keep both of their eyes and will survive. Germany's premier network, ZDF reported this story, which can be found on the link below (you can translate the text of the story into English using Google Translate):

http://www.zdf.de/volle-kanne/praxis-taeglich-app-als-fruehwarnung-vor-augenkrebs-39098494.html?tabNo=0

There are other examples of how CRADLE has helped children receive diagnoses of tough-to-spot eye diseases. This link in PEOPLE magazine describes a few examples:

http://www.people.com/article/dad-creates-app-detects-eye-cancer-children

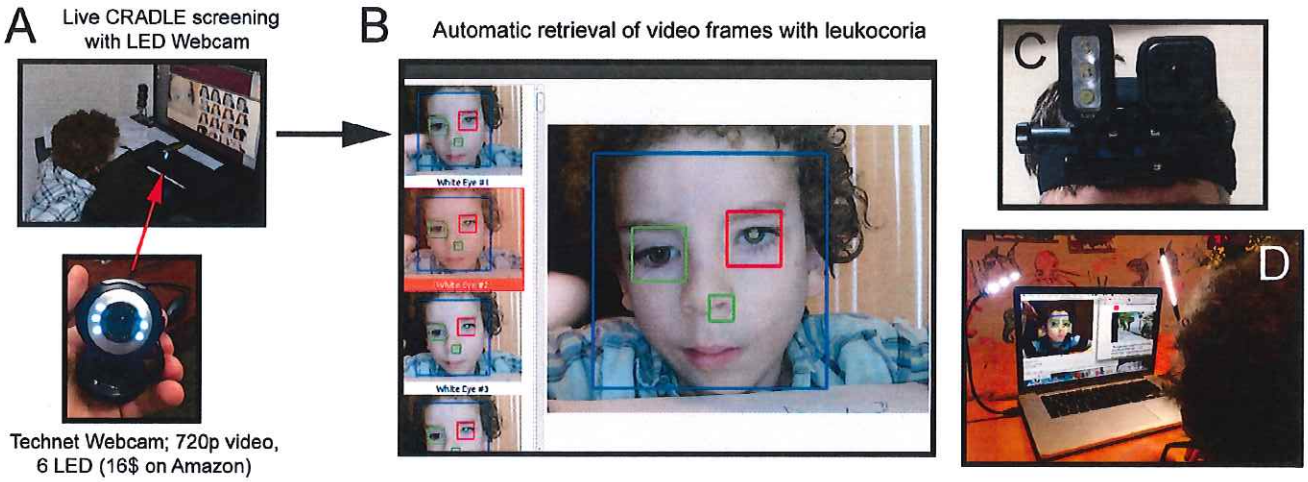

Figure 3. Different types of hands-free/live-video versions of CRADLE tested on retinoblastoma survivor with regressing tumors. A) A webcam equipped with 6 adjustable LEDs is used to screen for leukocoria in sitting position. B) This version of CRADLE removes and stacks leukocoric video frames in real time (allowing clinician to examine or store frame in the patient's electronic medical record). C) A POV "GoPro" camera with LED attachment. D) Laptop version of CRADLE using screen camera and USB-LED. Scanning the Rb survivor (left side of laptop screen) while his eye tracks cartoons (right side of laptop screen) allows testing at multiple optical axes. Images donated by Bryan Shaw.

Obstacles Encountered in Developing CRADLE. The largest obstacle we have encountered while developing CRADLE is receiving funding (e.g., from NIH) to further develop, optimize, and test CRADLE in clinical settings. We are hopeful that we will eventually receive funding. Receiving funding to clinically validate CRADLE is necessary for the development of this technology. We know that CRADLE works, but we want to know how well it works. We want to know: what is the smallest size tumor it can detect? Are tumors in the periphery more difficult to image than centrally located tumors? We want to test its efficacy at detecting other eye diseases. How early can it catch Coats' disease and cataract? What is the minimal refractive error that it can detect? Is CRADLE more effective and easier to use than the ophthalmoscope? Should doctors use CRADLE with the room lights on or off? How well does it work in outdoor settings? What are the optimum usage parameters? We also need to translate the text and instructions in CRADLE into every language possible. We want to receive FDA approval for CRADLE, in hopes that pediatricians will feel more comfortable recommending CRADLE to their patient's guardian. Four million children are born in the U.S. each year, and we cannot possibly reach out to all parents, year after year, in terms of advertising CRADLE. We can, however, reach all pediatricians in the U.S.—there are only ~ 30,000, with low turnover—and we believe that FDA approval will increase the chances that pediatricians recommend CRADLE to guardians of their new patients.

My research team and I have received little resistance from the oncology and ophthalmology community. Pediatric ophthalmologists and oncologists from Dana-Farber Cancer Institute, Massachusetts Eye and Ear Infirmary, Baylor College of Medicine and St. Jude Children's Research Hospital have enthusiastically become part of our research team, either by co-authoring peer reviewed studies regarding CRADLE, or collaborating as co-investigators on our grant applications to fund the clinical validation of CRADLE. Ophthalmologists and pediatricians whom we have no formal collaboration with have contacted us and informed us that they are testing CRADLE in their clinics across the world.

We have not encountered complaints of issues of privacy from our users. CRADLE has been designed so that it does not upload your pictures to us for analysis, rather it downloads itself to your phone, and you search your own pictures. This design also lets the user operate CRADLE without internet access (although internet access is needed to initially download CRADLE).