# Infrascanner White Paper

## Executive Summary

An estimated 1.4 million people experience Traumatic brain injury (TBI) each year in the United States, resulting in 1.1 million hospital visits, 235,000 hospitalizations and 50,000 deaths. TBI is a major public health problem among males ages 15 to 24, who account for two-thirds of childhood and adolescent head trauma patients. In addition, TBI is a severe problem among elderly people (age 75 years and older) of both sexes.

Rapid triage, diagnosis and treatment are critical in minimizing the adverse consequences of the more serious TBI cases. Since many TBI cases occur in clusters and are part of complex, extensive trauma to the individual victim (stemming from automobile accidents, war-zone explosions, etc.), the challenges presented to on-site medical personnel are significant. For patients with moderate-to-severe TBI in particular, diagnosis within the first hour (the "golden" hour) of the traumatic event is critical[1].

InfraScan, Inc. has developed the Infrascanner to provide a rapid evaluation of head trauma patients with possible intracranial hemorrhage. The technology is portable and noninvasive, allowing for repeated monitoring without concern for radiation dose. The development of the Infrascanner was sponsored by the Office of Naval Research (ONR) and the Marines Corps.

## Brain Injury Overview

A TBI, one of two subsets of acquired brain injury, can result from a closed head injury (whereby the head suddenly and violently hits an object but the skull remains intact) or a penetrating head injury; the other subset of acquired brain injury is non-traumatic brain injury (e.g., stroke, meningitis). A highly individualized injury, TBI severity depends on the nature of the injury, strength of the force, area of the brain affected as well as physical and genetic variations among patients. The damage from TBI can be localized (focal), confined to one area of the brain, or diffuse (typically a concussion), involving more than one area of the brain.

Types of focal brain injury include bruising of brain tissue (contusion) and rupture of blood vessels inside the skull, thereby resulting in heavy bleeding (intracranial hemorrhage or hematoma). Hemorrhaging can occur inside of the skull but outside of the brain (extra-axial) or within the brain itself (intra-axial). Extra-axial hemorrhages can be further divided into epidural hematoma, subdural hematoma and subarachnoid hemorrhage. Intra-axial bleeding within the brain itself is called an intracerebral hematoma.

Diagnostic and treatment protocols mandate that a patient suffering from head trauma receive immediate medical assessment, including a complete neurological examination. The severity of the head trauma and the responsiveness of the patient in a Glasgow Coma Scale (GCS) evaluation will determine which diagnostic methods will be used for further evaluation. In a GCS evaluation, the patient is scored on his/her ability to open eyes, communicate verbally and demonstrate motor skills. However, the GCS evaluation can be very subjective based upon the individual administering the test and can also be hampered if the patient is under sedation or has restrictions on his/her ability to verbally communicate (i.e., the patient has been intubated).

For patients with mild-to-moderate injuries, further diagnostic tests may be limited to skull and neck X-rays to check for bone fractures. For patients that have demonstrated moderate–to-severe TBIs after undergoing a neurological examination, the gold standard imaging test is a computed tomography (CT) scan, which creates a series of cross-sectional X-ray images of the head and brain and can show bone fractures as well as the presence of hemorrhage, hematomas, contusions, brain tissue swelling, and tumors. Magnetic resonance imaging (MRI), which uses magnetic fields to detect subtle changes in brain tissue content and can show more detail than X-rays or CT, may be used after the initial assessment and treatment of the TBI patient.

TBIs can cause a host of physical, cognitive, emotional, and social effects. And the outcomes for TBIs can be anything from complete recovery to permanent disability or death. An estimated 5.3 million individuals in the United States are living with long-term or life-long disability associated with a TBI that resulted in hospitalization. Unlike most causes of traumatic death, a large percentage of the people killed by brain trauma do not die right away but rather days to weeks after the traumatic event. In addition, rather than improving after being hospitalized, some 40% of TBI patients deteriorate.[2] Primary injury (the damage that occurs at the moment of trauma when tissues and blood vessels are stretched, compressed, and torn) is not adequate to explain this degeneration. Rather, the deterioration is caused by secondary injury resulting from a complex set of biochemical cascades that occur in the minutes to days following the trauma.[3] These biochemical cascades are instigated by brain swelling and inadequate flow of oxygen and blood to the brain resulting from brain compression by the expanding brain hematomas. The aim of the Infrascanner is to catch those hematomas before they are able to do any brain damage and lead to a much earlier intervention to evacuate the expanding brain hemorrhages.

In addition to disability, TBI can lead to increased risks for other debilitating health conditions. Recent studies indicated that in the 1 – 3 year post-injury period, individuals with TBI are 1.8 times more likely to report binge drinking, 11 times more likely to develop epilepsy and 7.5 times more likely to die. Additionally, the problems in the post-injury period include a 1.5 times higher risk for depression, and 2.3 times and 4.5 times higher risks for Alzheimer's disease associated with moderate and severe head injuries, respectively.[4]

## Types of Intracranial Hematomas after Traumatic Brain Injury

Injury to the brain after trauma can be classified as focal or diffuse. Focal mass lesions are less common, but the importance of appropriate and timely surgical treatment is emphasized by the significantly poorer outcome associated with mass lesions. In the Traumatic Coma Data Bank (TCDB) series[5], the mortality rate after severe closed head injury was 39% with a focal lesion, compared to 24% with a diffuse injury. There are 3 major types of traumatic intracranial hematomas: (1) subdural, (2) epidural, and (3) intracerebral hematomas. Each of these lesions has characteristic clinical and CT scan findings, and can be present on admission to the hospital or can occur in a delayed fashion.

(1) Subdural Hematoma.

The subdural hematoma is the most common focal intracranial lesion, occurring as the primary initial lesion in 24% of patients with severe closed head injuries in the TCDB[5], and occasionally as a delayed lesion. The hematoma is between the dura and the brain, usually resulting from a torn bridging vein between the cortex and the draining sinuses. An acute subdural hematoma typically appears on a CT scan as a high-density, homogenous crescent-shaped mass paralleling the inner surface of the skull.

Most acute subdural hematomas require surgery. Despite surgical evacuation, the mortality rate in patients with subdural hematomas was 50% in the TCDB series. The rapidity of surgical evacuation and the degree of associated brain damage are major determinants of outcome. Several studies report a decrease in the early mortality or morbidity in patients who underwent an early evacuation of subdural hematoma.

(2) Epidural Hematoma.

Epidural hematomas, or collections of blood between the skull and dura, are less common, occurring as the primary initial lesion in 6% of patients with severe closed head injuries in the TCDB series[5]. Epidural hematomas can be present on the admission CT scan or less commonly may develop at some later time. In a consecutive series of 161 patients with epidural hematoma, 8% had delayed formation of the hematoma[6]. The delayed epidural hematoma can develop after evacuation of a hematoma on the opposite side or after a hypotensive patient has been resuscitated. In addition, epidural hematomas can recur after surgical evacuation. In a study of 88 patients with post-operative hematomas, 47 patients with an epidural hematoma developed a post-craniotomy hematoma requiring a second surgical procedure[7].

Although patients with subdural hematomas are usually immediately comatose, only a third of patients with an epidural hematoma are unconscious from the time of the injury, one third have a lucid interval, and one third are never unconscious. An epidural hematoma is almost always associated with a skull fracture (91% in adults, and 75% in children)[8]. The blood comes from torn dural vessels, usually arterial, from the fractured skull bone, or occasionally from torn venous sinuses. On CT scan, an epidural hematoma is characterized by a biconvex, uniformly hyperdense lesion. Associated brain lesions are less common than with subdural hematomas.

Most epidural hematomas require surgery, and mortality and morbidity of surgical evacuation is low if the patient is operated upon early. The outcome of the patient with an epidural hematoma depends on the neurological status at the time of surgery. The mortality rate varies from 0% for patients who are not in coma, to 9% of obtunded patients, to 20% for patient in deep coma.

(3) Intracerebral Hematoma.

Intracerebral blood can take the form of a hematoma or a contusion. Intracerebral hematomas are more common, occurring as the primary lesion in 10% of the severe closed head injuries in the TCDB series[5]. Most intracerebral hematomas are visualized on CT scan as hyperdense mass lesions. They are typically located in the frontal and temporal lobes and can be detected on a CT scan immediately after the trauma. However, delayed intracerebral hematomas may also be manifest during the hospital course. A delayed hematoma is one that is seen on a repeat CT scan within 24 to 48 hours of the injury or operation but is not present on the initial CT scan. Commonly, a delayed hematoma is associated with clinical deterioration.

Hemorrhagic contusions were present as the primary lesion in 3% of severe closed head injuries in the TCDB series[5]. Single contusions are located either below the region of the impact or opposite the region of impact. Contusions appear as heterogeneous areas of brain necrosis, hemorrhage, and infarct representing mixed-density lesions on CT scan. Multiple focal contusions have a "salt and pepper" appearance on CT scan.

The decision to operate on an intracerebral hematoma is based on the patient's general condition, associated brain injuries, site and size of the hematoma, the ICP, and the magnitude of the mass effect. Generally accepted indications for surgery include (1) a hematoma associated with mass effect or in the

anterior temporal lobe or in the cerebellum, (2) progressive neurological deterioration, or (3) refractory intracranial hypertension.
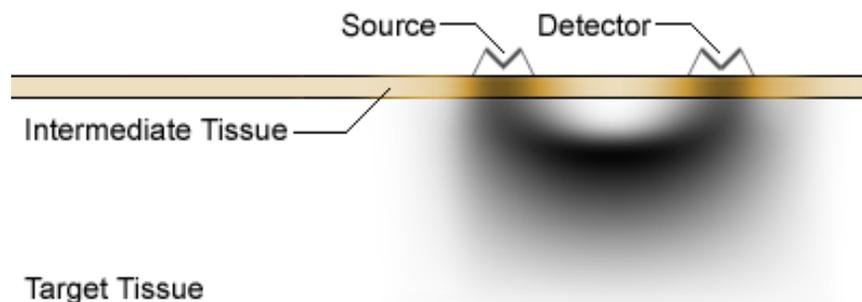
<u>Delayed Intracranial Hematomas</u>

Delayed intracranial hematomas are a treatable cause of secondary injury if identified early, but can cause significant disability or death if not promptly recognized and treated. CT scanning has revealed that delayed hematomas after head trauma are more common than had been previously suspected. Recurrent hematomas, postoperative epidural hematomas, and delayed traumatic intracerebral hematomas occur in up to 23% of patients with severe head injury. Mortality rates and the incidence of a poor neurological recovery are significantly increased in patients who develop delayed traumatic intracranial hematomas. Early identification, prior to neurological deterioration, is the key to successful surgical treatment.

Serial CT scans are the most reliable method for detecting a delayed hematoma. However, CT scans require that patients, many of whom are critically ill, be taken out of the intensive care unit, and the yield is relatively low if serial scans are obtained in all patients. Some clinical monitoring technique for accurate selection of patients requiring follow-up CT scanning would improve the yield. Nevertheless, current clinical monitoring techniques are not ideal for detecting delayed hematomas. Patients with delayed hematomas may appear to be relatively normal only to undergo sudden neurological deterioration, or may not exhibit a change in their neurological examination. Intracranial pressure (ICP) may be normal in up to 20% of patients harboring delayed hematomas that require surgery.

The ideal clinical monitor would be capable of making on-line continuous measurements in the intensive care unit, and would identify the development of a hematoma prior to the onset of clinical neurological deterioration. The technique of near-infrared spectroscopy (NIRS) may have these characteristics.

## Science and Technology

All biological tissue is, to differing extent, permeable to electromagnetic radiation of different frequencies and intensities. This can also be considered permeability to photons of different energy levels. This permeability to electromagnetic energy is the basis of all imaging based on transmission/scattering characteristics such x-ray, Computed Tomography, and near-infrared, NIR, imaging. From the principles of spectroscopy, it is also known that different molecules absorb different wavelengths of electromagnetic radiation (which is synonymously referred to as light at shorter wavelengths). Similarly, tissue scatters radiation to different degrees. The Infrascanner is concerned with NIR imaging of the hemoglobin molecules. From any light source, photons follow a characteristic path through the target tissue back to a detector on the same approximate plane as the source. While the light is severely attenuated due to the scattering and absorption process, it is nonetheless encoded with the spectroscopic signatures of the molecules encountered en route to the detector.



**Simulated photon diffusion path through target tissue from source to detector.**

The principle used in identifying intracranial hematomas with the Infrascanner is that extravascular blood absorbs NIR light more than intravascular blood. This is because there is a greater (usually 10-fold) concentration of hemoglobin in an acute hematoma than in normal brain tissue where blood is contained within vessels. The Infrascanner compares left and right side of the brain in four different areas. The absorbance of NIR light is greater (and therefore the reflected light less) on the side of the brain containing a hematoma, than on the uninjured side. With specified wavelength ranges, optical light source(s) or emitter(s) and a photodetector are placed at a distance, which allows proper NIRS absorption measurements in a desired volume of tissue. The wavelength of 805nm is sensitive only to blood volume, not to oxygen saturation in the blood, as shown in the figure below.
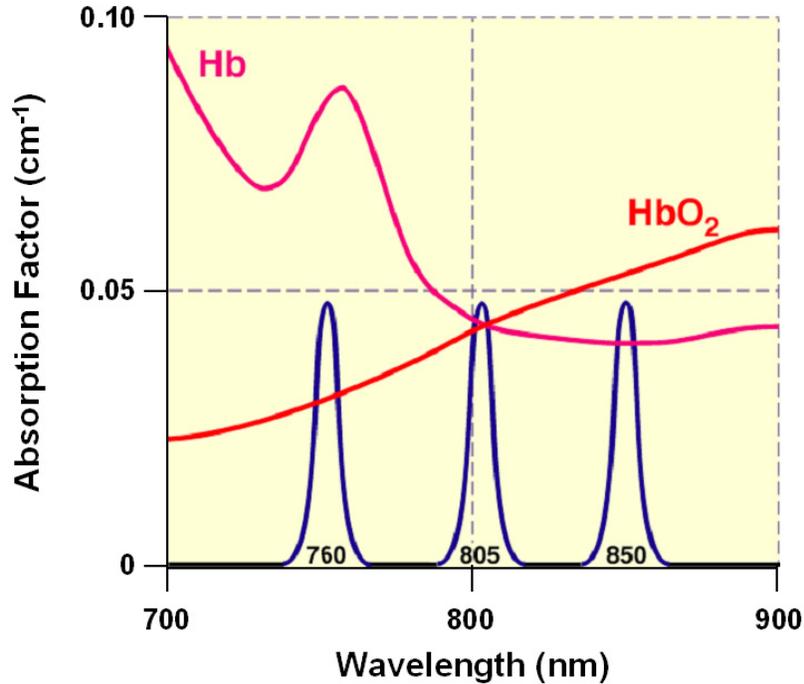


**Absorption of light by oxygenated and deoxygenated hemoglobin**

The Infrascanner is placed successively in the left and right frontal (F), temporal (T), parietal (P), and occipital (O) areas of the head and the absorbance of light is recorded. The difference in optical density (ΔOD) in each of the four symmetrical areas is calculated on a pair-wise basis from the following formula:

$$\Delta OD = \log_{10}\left(\frac{I_N}{I_H}\right) = \log_{10}(I_N) - \log_{10}(I_H)$$

where $I_N$ = the intensity of reflected light on the normal side, $I_H$ = the intensity of reflected light on the hematoma side.
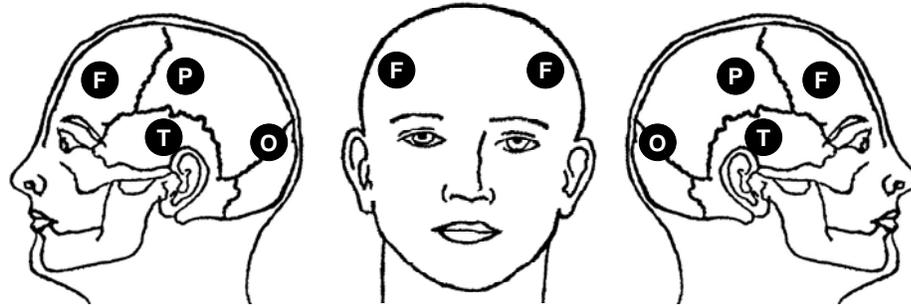
**Head location of Infrascanner measurements**

**F**rontal      Left/Right forehead, above the frontal sinus
**T**emporal    In the Left/Right temporal fossa
**P**arietal      Above the Left/Right ear, midway between the ear and the midline of the skull
**O**ccipital    Behind the Left/Right ear, midway between the ear and the occipital protuberance

# The Device



**Infrascanner Model 2000**

The Infrascanner includes three components: (1) the Scanner, (2) the Disposable Shield and (3) a Cradle. The Scanner includes a safe NIR diode laser and a silicon detector. The light to and from the laser and detector are optically coupled to the patient's head through the disposable shield optical fibers. The optical fibers are long enough to reach through hair and contact the scalp. The optical fibers are placed 4 cm apart allowing optimal detection of hematomas. The extended fiber optics eliminates the need to shave off any hair. And because the fiber optic piece is disposable it prevents cross contamination. The

detected light passes through an optical NIR bandpass filter in order to minimize background light interference. Electronic circuitry is included to control laser power and the detector signal amplifier gain. The detector signal is digitized and analyzed by a single board computer, SBC, in the Scanner. The SBC receives the data from the detector and automatically adjusts the settings of the Scanner to ensure good data quality. The data is further processed by the SBC and the results are displayed on the screen. Readout of the scan provides information on the severity of a hematoma and identifies the region of the brain bleeding. A higher optical density in the scanned region indicates a larger hematoma.

# Clinical Data

In a pilot study[9], a NIRS examination was obtained in the ER at the time of the admission CT scan. Using an early prototype of the Infrascanner, called the "Runman", serial measurements of ΔOD were obtained in 305 head-injured patients. The maximal ΔOD among the various regions examined was recorded for each patient and was correlated with the admission CT scan. ΔOD on admission to the hospital was significantly elevated (>0.05) in all but 4 (2%) patients with intracranial hematomas. ΔOD was normal (0.00-0.05) in patients with diffuse brain injury (DBI). A single NIRS examination therefore reliably identified patients with an intracranial hematoma (98% had a ΔOD > 0.05), and gave a suggestion of whether the hematoma was intracerebral (most had a ΔOD <0.6) or extracerebral (most had a ΔOD >0.6).

The pivotal double blinded clinical study for FDA clearance[10] was carried out in five different clinical sites four of which are in the U.S: (1) Baylor College of Medicine, (2) Hahnemann Hospital, (3) The Hospital of the University of Pennsylvania and (4) University of Cincinnati. The fifth site was the Lokmanya Tilak Memorial General Hospital located in India. Clinical personnel in these five sites collected data using the Infrascanner and Computer Tomography (CT) scans (the gold standard in detecting hematomas). All the CT scans were read by the expert radiologist from an independent site, John's Hopkins University Hospital. The evaluation of the Infrascanner measurements in comparison to the CT scans is based on a total of 431 patient data where 122 of them were hematoma cases of various sizes, depths and places. Study results address the hematomas that clinicians may expect the Infrascanner to detect in the clinical practice setting. Consistent with preclinical testing, the Infrascanner demonstrated high sensitivity (88%) in detecting hematomas > 3.5cc in volume and < 2.5 cm from the surface of the brain. Specificity in the Per Protocol population was 91%. The balance between specificity and sensitivity supports the utility of the Infrascanner to prioritize patients with suspected hematomas for CT scan. It should be noted that the device is indicated for use as a screening tool and as an adjunct to the standard diagnostic workup and will not be used in lieu of this workup.

An adult population study in Seville, Spain[11], evaluated a total of 35 TBI patients, ages 17-76 years. There were 19 intracranial hematomas, confirmed by a CT scan completed on all subjects within 40 minutes of the Infrascanner test. The Sensitivity in this population was 89.5% and Specificity was 81.2%.

A study in Pittsburgh[12] evaluated in Pediatric ICU 28 patients of 0-14 years who underwent CT as part of the clinical care not necessarily triggered by trauma. There were 12 intracranial hematomas, confirmed by a CT scan completed on all subjects within 24 hours of the Infrascanner test. The Sensitivity in this test was 100% and Specificity was 80%.

A study in Padua and Treviso, Italy,[13] evaluated 110 children at intermediate or high risk for intracranial injury according to the PECARN rules (GCS 14 and 15). There was only one brain hematoma case in this

group (it was successfully detected). The Specificity in this test was 93% and the NPV was 100 %. The use of Infrascanner would have led to avoid ten CT scan, reducing the CT scan rate by 58.8 %

A study in Lublin, Poland,[14] evaluated 94 children with mild TBI (GCS 14 and 15). The Sensitivity in this test was 86.7 % and Specificity was 90 %. The aim of the study is to propose a new protocol of screening patients using Infrascanner as a complement to repeated neurological examination and medical history review.

A study by the German Army doctors in Kunduz, Afghanistan[15], evaluated a total of 11 TBI patients (military personnel and local civilians). There were no intracranial hematomas in this group, as was confirmed by a later CT scan in Mazar-e-Sharif. The Specificity in this test was 100%. The user evaluation showed that the Infrascanner allows a preliminary estimate of an intracranial hematoma and that Infrascanner is easy to learn and can be repeatedly used even under emergency room conditions.

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