Thermal Flow Detection Improves Diagnostic Accuracy of Shunt Malfunction: A Prospective, Multicenter, Operator-Blinded Study

David M. Frim MD PhD[7] and Joseph R. Madsen MD[1] for the ShuntCheck Study Group; [Tehnaz P. Boyle MD PhD[2], Mark I Neuman MD MPH[1], Mandeep S. Tamber MD PhD[3], Robert W. Hickey MD[3], Gregory G. Heuer MD[4], Joseph Zorc MD MSCE[4], Jeffery R, Leonard MD[5], Julie C. Leonard MD MPH[5], Robert Keating MD[6], James Chamberlain MD[6], Paula Zakrzewshi RN MSN[7], Petra Klinge MD PhD[8], Lisa H. Merck MD MPH[8], Joseph H. Piatt MD[9], Jonathan E. Bennett MD[9], David I. Sandberg MD[10], Frederick A. Boop MD[11]]

1Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts; [2]Current Address: Boston Medical Center, Boston, Massachusetts; [3]Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania; [4]Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; [5]Nationwide Children's Hospital, Columbus, Ohio; [6]Children's National Medical Center, Washington, DC; [7]University of Chicago Children's Hospital, Chicago, Illinois; [8]Rhode Island Hospital, Providence, Rhode Island; [9]DuPont Children's Hospital, Wilmington, Delaware; [10]University of Texas Houston Children's Hospital, Houston, Texas; [11]LeBonheur Children's Hospital, Memphis, Tennessee

***Objective*:** ShuntCheck® is a novel, non-invasive device that uses a thermal gradient to rapidly assess cerebrospinal fluid (CSF) flow in a shunt. CSF is cooled transcutaneously by an instant cold pack where the shunt catheter crosses the clavicle. CSF flow within the shunt is detected if a temperature drop is measured distally. We evaluated the diagnostic value of thermal flow detection in ventriculoperitoneal shunts to determine whether ShuntCheck plus neuroimaging improved diagnostic precision over imaging alone. Additionally, we compared the rule-out accuracy of ShuntCheck to neuroimaging in children assessed clinically as low risk for malfunction.

Methods: Thermal flow detection and ventricular imaging by CT or MRI were obtained in 211 symptomatic patients $\leq$ 29 years old at ten centers. Clinicians, blinded to the results of the ShuntCheck test, tabulated whether radiographic studies showed ventricular enlargement, and whether surgery for obstruction was performed over the next week. The diagnostic utility of imaging alone, and the combination of ShuntCheck plus imaging, were calculated as both positive and negative predictive values (PPV and NPV). Patients were classified as "low-risk" if judged by the evaluating ED Attending physician or Neurosurgical resident prior to neuroimaging as "Unlikely to require neurosurgery".

Results: Imaging alone had a PPV of 57.9% (22/38 cases, 95% confidence interval 42.3-72.2%). ShuntCheck, when concordant and positive (flow not confirmed, with ventricular enlargement) showed a PPV of 88.0% (22/25 cases, C.I. 70.0-95.8%) Of 97 patients with both studies negative (flow confirmed and no ventricular enlargement), zero went on to surgery (NPV 100%, C.I. 96.2-100%). For imaging alone, the NPV was 96.0% (166/173, C.I. 91.9-98.1%). The improvement in PPV of 30.1% (C.I. 9.9-50.3%) and NPV of 4.0% (C.I. 1.3-7.2%) is significant. Within the imaging negative patients, taken alone, and the image positive patients, taken alone, the ShuntCheck results significantly improved clinical outcome prediction ($p<.003$, Fisher's exact test, two-tailed). 66% of patients were classified "low risk". This assessment was accurate in 92% of these cases. ShuntCheck (NPV 100%) was not inferior to neuroimaging (NPV = 97.3%) in confirming this clinical judgment (risk difference 2.7%; 95% confidence interval, .998-1.057).

70 patients who were assessed as low risk and had confirmatory ShuntCheck Flow reading went on to have 70 imaging studies, 13 hospital admissions for observation and 2 lumbar punctures but no shunt surgeries. An additional 38 patients who had concordant reassuring studies (with the radiographic studies only available to the clinical team) went on to have 8 hospital admissions for observation, 1 radionuclide study and 2 surgeries which uncovered no obstruction.

Conclusion: The combination of neuroimaging and ShuntCheck improves shunt malfunction diagnostic accuracy and may diminish the need for hospital admission, additional invasive tests, and avoidable surgeries. ShuntCheck was not inferior to neuroimaging for ruling out shunt malfunction in children assessed as "Unlikely to require surgery" and may obviate the need for neuroimaging amongst these patients thereby reducing radiation exposure.

Keywords: hydrocephalus, noninvasive, flow detection, shunt

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I. Background

Hydrocephalus is a condition of abnormal cerebrospinal fluid (CSF) homeostasis, resulting in an accumulation of CSF in the brain ventricles. The most common treatment for hydrocephalus is diversion of CSF from the brain ventricles to the peritoneal cavity by means of a permanent prosthetic shunt. Shunt failure, usually by obstruction, is common [1-6], but the symptoms of shunt obstruction (headache, nausea, lethargy) are non-specific, resulting in three false alarms in the emergency department for every true shunt malfunction [7]. Computed Tomography (CT) remains the standard test for shunt obstruction but radiation exposure from repeat CT scans is a recognized and growing concern among neurosurgeons [8].

ShuntCheck is a new, non-invasive device which uses thermal dilution to assess CSF shunt flow. An open label study of ShuntCheck at Boston Children's Hospital found high sensitivity but weaker specificity, yielding strong Negative but weak Positive Predictive Values. This contrasts with CT Scans which have moderate sensitivity and high specificity, yielding strong Positive but weaker Negative Predictive Values. This contrast led to two potential diagnostic uses for ShuntCheck. ED MDs observed that many patients presenting in the ED were judged to be at low risk for shunt malfunction but rule out required a confirmatory test. Given its strong sensitivity and Negative Predictive Value, if ShuntCheck proved to be equivalent to CT Scan as a confirmatory rule out test for these low risk case, it could become a viable alternative and reduce the number of CT exposures for these patients. Our first hypothesis became: ShuntCheck's NPV is equal (non-inferior) to CT NPV in ruling out shunt obstruction in patients clinically judged by the Attending Physician to be "unlikely to require shunt surgery". Also observed was that many suspected shunt malfunction cases required admissions for observation or invasive testing in addition to imaging. The contrasting strengths and weaknesses of ShuntCheck vs CT suggested that the two tests might be synergistic. Our second hypothesis became: concordant ShuntCheck and CT results would have higher PPV and NPV than CT alone

To test these two hypotheses, we evaluated the ShuntCheck device in symptomatic pediatric and young adult patients. ShuntCheck tests were conducted on a blinded basis. Patients received Standard of Care (SOC) diagnostic procedures. Clinical outcome (surgical revision of shunt or discharge without surgical revision) was confirmed after 7 days by calling the subject and/or the care provider/physician in charge. If surgery was conducted, the neurosurgeon completed a questionnaire providing intra-operative evaluation of shunt patency and/or blockage. ShuntCheck and SOC diagnostic results were compared to patient outcomes.

II. Patient Selection and Methods

Testing technique: Informed consent was obtained prior to performing the ShuntCheck test, which included informing subjects that test results would not be made available to the clinical team, the patient, or family. ShuntCheck tests were done with the patient in either a sitting (preferred) or supine (where necessary) position. Following the device manufacturer's recommendations, an adhesive patch with three temperature sensors was placed on the skin, over the clavicle, so that the middle sensor was over the shunt while the two remaining sensors, serving as controls, were positioned symmetrically on each side of the shunt.(Figures 1 & 2) The sensor patch was then connected by electric cable to the ShuntCheck Data Acquisition Unit (DAQ) which, in turn was connected to a Windows Tablet computer running ShuntCheck software. A commercially

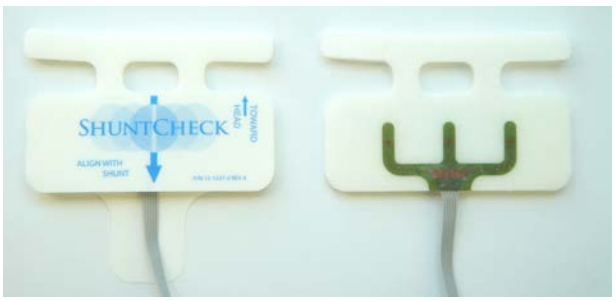


Figure 1 ShuntCheck sensor front (left) and back (right). Thermistor temperature sensors are on the tips of the E shaped circuit

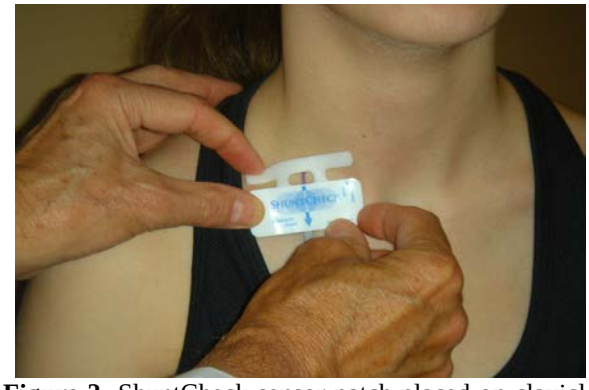


Figure 2 ShuntCheck sensor patch placed on clavicle centered over shunt catheter

available instant cold pack was applied two times to the skin on the neck just above the sensor patch (Figure 3) – on for 60 seconds, off for 120 seconds, on for 120 seconds.

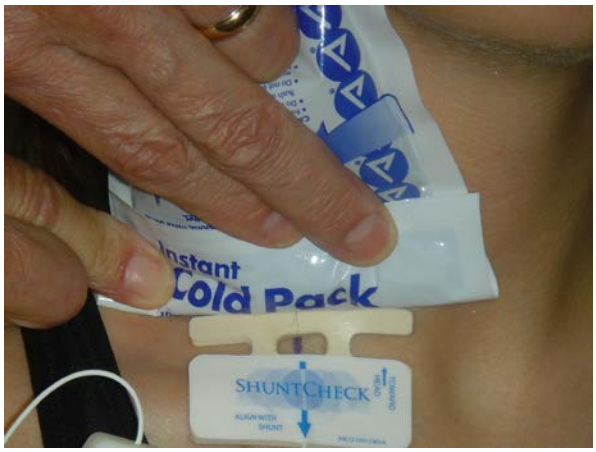


Figure 3 Instant ice pack application "upstream" o f the ShuntCheck sensor patch

When there is flow in the shunt, cooled CSF flows beneath the sensor, which results in a measurable temperature drop in the central sensor with respect to the two control sensors (Figure 4); absence of flow results in little difference in temperatures detected by all three sensors. The ShuntCheck device directs timing of application and removal of the ice pack and records temperature readings from all three sensors from 10 seconds pre-ice (to establish a baseline) to nine minutes post ice application. In all cases, data was collected using the tablet computer which detects flow via an algorithm which interprets the time-temperature data. The algorithm first calculates a temperature curve T(t), where t represents time, by computing for each time point the temperature difference between the middle sensor and the mean of the two controls. Next, a difference ΔT between the maximal and minimal values of T(t) is calculated. Finally, a conclusion is made with regard to presence or absence of flow: ΔT has to be above a predetermined threshold the device reports for flow result to be established.

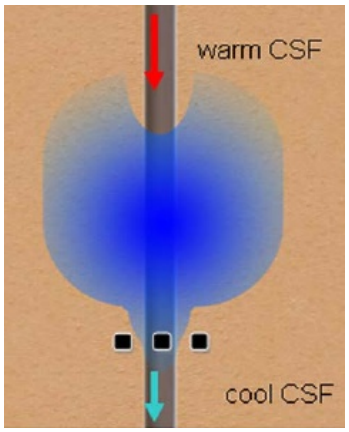


Figure 4: Depiction of CSF flow through cold "zone" and flow of chilled CSF to center thermistor

The algorithm that classifies the collected data into categorical readings of "flow confirmed" (FC), or "flow not confirmed" (FNC), was based on previous animal and pilot clinical tests done with the same device [12]. The algorithm assumes that a concave U-shaped temperature curve with ΔT of at least 0.2° Celsius (Figure 5) is required for confirming flow; any other temperature curve will result in not confirming flow. Test results (the time-temperature graph and the FC/FNC determination) were uploaded to the device manufacturer blind to any clinical information.

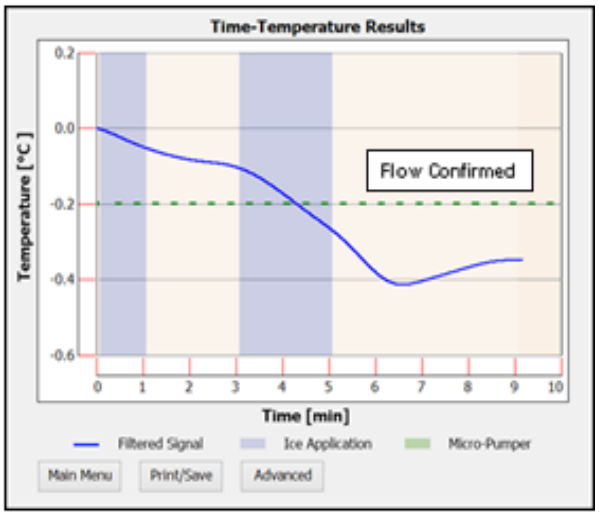


Figure 5 ShuntCheck results screen time-temperature graph showing flow-related temperature drop. The blue bars note ice placement timing. The green dotted line at 0.2°C marks the threshold for "Flow Confirmed"

Patient selection: Patients age 3-29 with symptoms sufficient to warrant diagnostic testing were recruited into the study. Patients with multiple catheters, edema over the shunt, or where ShuntCheck testing would interfere with care were excluded. Enrolled patients were typically tested with ShuntCheck in the emergency department. 196 patients completed ShuntCheck testing and received neuroimaging (either CT Scan or MRI).

Clinical Endpoints: Subjects enrolled in this study were scored as to whether they required shunt revision surgery within seven days of the test. For patients who went to surgery, a determination that the shunt had no observable CSF flow was made when the shunt was disconnected, possessed complete lack of observable flow, exhibited flow of less than 2 drops in 20 seconds from above the disconnection, or obstruction of distal flow when checked with a manometer. A determination of likely having patent flow was defined as CSF flow at six drops per minute with a patent system downstream by manometry (even if one or more components were revised for partial obstruction). 32 patients or 15% of the group actually went on to operative exploration. 29 of these surgeries confirmed complete or partial

shunt obstruction. 3 surgeries concluded "no obstruction" and these patients were classified as having "True Negative" outcomes. No cases were scored as "indeterminate".

Statistical Analysis: Binary outcome event (FC vs. FNC; Imaging Unchanged/Decreased/Not Suggestive of Malfunction vs Enlarged/Suggestive of Malfunction, Shunt obstruction confirmed by surgery vs. no surgery or no obstruction confirmed by surgery) were summarized in standard diagnostic 2x2 matrices to compute Sensitivity, Specificity, Positive and Negative Predictive Values (PPV and NPV). The difference, ratio, and 95% confidence intervals were calculated to estimate the effect of the specificity and sensitivity of ShuntCheck + Imaging to that of imaging alone. In addition, the PPV and NPV of ShuntCheck + Imaging was compared to the PPV and NPV of Imaging alone using similar methods. These results were computed using SAS v9.2 software (SAS, Institute, Cary, North Carolina).

This research study was done under a research protocol approved by the Institutional Review Boards of each of the study sites.

III. Results

Sensitivity, Specificity, Positive and Negative Predictive Values: ShuntCheck generated strong Sensitivity (100%) and Rule Out/NPV (100%) and weak Specificity (60%) and Rule In/PPV (29%) performance:

	ShuntCheck Dx 2x2 Matrix		
	Actual Blocked Shunts 29 Patients	Patent Shunts 182 Patients	
ShuntCheck FNC (Positive Test)	True Positives 29 Patients	False Positives 72 Patients	Rule In (PPV) 29%
ShuntCheck FC (Negative Test)	False Negatives 0 Patients	True Negatives 110 Patients	Rule Out (NPV) 100%
	Sensitivity 100%	Specificity 60%	

Neuroimaging exhibited a different pattern – moderate Sensitivity (76%) but strong Specificity (91%):

	Imaging Dx 2x2 Matrix		
	Actual Blocked Shunts 29 Patients	Patent Shunts 182 Patients	
Imaging Enlarged (Positive Test)	True Positives 22 Patients	False Positives 16 Patients	Rule In (PPV) 58%
Imaging Normal (Negative Test)	False Negatives 7 Patients	True Negatives 166 Patients	Rule Out (NPV) 96%
	Sensitivity 76%	Specificity 91%	

ShuntCheck-Imaging Concordant Results: This may explain the diagnostic synergy of ShuntCheck plus Imaging. When the two methods generated concordant results (in 58% of cases), Sensitivity, Specificity, PPV and NPV rose:

	Concordant Dx 2x2 Matrix		
	Actual Blocked Shunts 22 Patients	Patent Shunts 100 Patients	
ShuntCheck FNC + Imaging Enlarged (Positive Test)	True Positives 22 Patients	False Positives 3 Patients	Rule In (PPV) 88%
ShuntCheck FC + Imaging Normal (Negative Test)	False Negatives 0 Patients	True Negatives 97 Patients	Rule Out (NPV) 100%
	Sensitivity 100%	Specificity 97%	

These concordant results are superior to Imaging alone results:

	Concordant vs Imaging Results Comparison		
	ShuntCheck + Imaging Concordant Results	Imaging Alone Results	PPV/NVP Improvement
PPV	88.0% (22/25) (95% CI 70.0-95.8%)	57.9% (22/38) (95% CI 42.2-72.2%)	30.1% (95% CI 9.9-50.3%)
NPV	100% (97/97) (95% CI 96.2-100%)	96.0% (166/173) 95% CI 91.9-98.1%)	4.0% (95% CI 1.3-7.2%)

Of course, rather than considering concordant patients as a special group, it may make more sense to determine the added value in probability terms among imaging negative and imaging positive patients. The contingency tables among these groups follows. It is interesting to note how ShuntCheck's strong Negative Predictive Value boosts Specificity among the Imaging Positive patient segment.

Within Imaging Negative (173 Patients)

	Occluded	Patent	Sensitivity	Specificity
ShuntCheck Positive	7	69	100%	58%
ShuntCheck Negative	0	97		

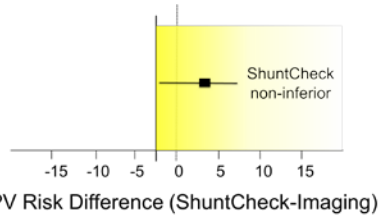
Within Imaging Positive (38 Patients)

	Occluded	Patent	Sensitivity	Specificity
ShuntCheck Positive	22	3	100%	81%
ShuntCheck Negative	0	13		

These are both very significant distributions (Imaging Negative p = .0027, Imaging Positive p<.0001, Fisher's Exact Test, two tailed

ShuntCheck NPV vs Imaging NPV in Patients "Unlikely to require surgery": Attending Physicians clinically assessed most patients (before imaging results were available) as either "Unlikely to require surgery" or "Somewhat likely or likely to require surgery". 192 patients received an assessment (23 patients did not because imaging results were available before the assessment could be made). 126 patients were judged to be Unlikely to require surgery – 66% of patients who were assessed. Clinical judgment was correct in 116 (92%) of these cases.

ShuntCheck tests of "Unlikely…" patients generated an NPV of 100% (70/70, 95% CI 94.8-100%). Imaging generated an NPV of 97% (109/112, 95% CI 92.4-99.1%). ShuntCheck therefore exceeded its a priori non-inferiority margin of -2.5%:



Admissions for Observation and Additional Invasive Testing: Patients admitted for observation and additional test procedures were recorded. 54 patients received additional procedures - 47 patients were admitted for observation, 3 patients received lumbar punctures, 7 received shunt taps and 8 received radionuclide shunt-o-gram tests. In each case, these invasive tests were conducted in addition to neuroimaging, suggesting that imaging results in 56 patients (27% of total patients receiving imaging) were inconclusive.

As reported above, 70 imaged patients were judged to be Unlikely to require surgery and received a ShuntCheck result of Flow Confirmed, a 100% NPV combination. 13 of these patients were admitted for observation and 2 received lumbar punctures. These 70 patients could have been ruled out via judgment confirmed by ShuntCheck, avoiding the imaging, admission, and LPs.

Similarly, 97 patients received concordant ShuntCheck plus Imaging negative results, a 100% NPV combination. 19 were admitted for observation, 3 received invasive testing and two underwent avoidable surgery. Eliminating overlap, 8 patients received additional care.

Surgery with No Obstruction: Three patients had surgical findings of "No Obstruction". Two of these surgeries would have been prevented via ShuntCheck-Imaging concordant negative results.

IV. Discussion

ShuntCheck's strong Sensitivity/NPV and weak Specificity/PPV shapes its role in shunt obstruction diagnosis.

ShuntCheck "Flow" is a strong indicator of shunt patency

- When combined with the Attending's judgment of "Unlikely to require surgery" NPV reaches 100% and represents a viable alternative to Imaging as a confirmatory rule out test, reducing the radiation exposure of CT Scans and the need for admissions for observation and additional invasive testing in 37% of cases.
- When combined with a negative Imaging result, NPV also = 100% and can result in a reduction in admissions for observation and additional invasive testing.

ShuntCheck Flow Not Confirmed is a very weak rule-in result – it might be described as a "non-negative" result. It is primarily valuable when combined with a positive Imaging result:

- ShuntCheck FNC + Imaging Enlarged resulted in a PPV of 88% compared with Imaging alone of 58%

V. Conclusions

The combination of neuroimaging and ShuntCheck improves shunt malfunction diagnostic accuracy and may diminish the need for hospital admission, additional invasive tests, and avoidable surgeries. ShuntCheck was not inferior to neuroimaging for ruling out shunt malfunction in children assessed as "Unlikely to require surgery" and may obviate the need for neuroimaging amongst these patients thereby reducing radiation exposure).

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