HeartLogic™
Heart Failure Diagnostic
In-Service
Heart failure is a major clinical concern that impacts patients’ quality of life and healthcare economics.

Heart failure hospitalizations are associated with an 8-fold increase in mortality and a 9-fold increase in recurrent hospitalizations\(^1\)

HF hospitalizations are the biggest outflow of money

- Accounting \(\approx 60\%\) of healthcare expenditure\(^2\)


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Symptoms can vary in presentation and time course, nevertheless, several patterns may precede a decompensation.
Boston Scientific sensors enable the early detection of heart failure decompensation symptoms

Sensors are intended to represent typical in-office tests and questions

<table>
<thead>
<tr>
<th>Our sensors:</th>
<th>What Clinicians ask/do during a physical exam</th>
</tr>
</thead>
<tbody>
<tr>
<td>🎧 Heart Sounds ___________________________</td>
<td>Listen to the heart S3 heart sound</td>
</tr>
<tr>
<td>🎧 Heart Sounds ___________________________</td>
<td>Listen to the heart S1 heart sound</td>
</tr>
<tr>
<td>🎧 Thoracic Impedance _________________</td>
<td>Take chest X-ray for signs of pulmonary edema</td>
</tr>
</tbody>
</table>
| 🎧 Respiratory Rate _____________________ | "Are you out of breath? Have difficulty breathing?"
| 👟 Activity Level ________________________ | "Are you able to get your mail/go upstairs?"
| 📊 Weight ______________________________ | "Have you gained weight?" (check leg or abdominal swelling) |
| 🎯 Night Heart Rate _____________________ | Is resting heart rate elevated? |

Key:
- New to Resonate Platform
- Legacy Trends
- Unique to BSC
Introducing HeartLogic™
Heart Failure Diagnostic

HeartLogic™ enables **proactive care** of heart failure patient management with a multifactorial approach

- Incorporates Multiple Sensors with a Single Composite Alert
- Available on LATITUDE NXT for patients with Resonate™ family of ICDs & CRT-Ds

The MultiSENSE study results¹ demonstrated:
**High sensitivity** of 70 % for detecting heart failure events
**Weeks of advance notice** of a potential heart failure event
**Low burden** of less than 2 alerts per patient per year.

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Benefit of Multifactorial Approach

Two Observed Cases

Patient A

Patient B

Which patient had a Heart Failure Event?

HeartLogic™

MultiSENSE Study

Case Studies
Benefit of Multifactorial Approach

HeartLogic™

Patient A — *Two Observed Cases* — Patient B

Multi-sensor Changes before a **HF Event**

Impedance-only Change with **NO Event**

HeartLogic Uses Multiple Sensors
HeartLogic™ Heart Failure Diagnostic

HeartLogic was validated to detect the early warning signs of worsening heart failure by combining data from 5 sensors into a single composite index.

Multiple Sensor Measurements

Heart Sounds S1 & S3
Impedance Thoracic
Respiration Rate & Volume
Activity Time Spent Active
Heart Rate Night

Combined into a single, simple index with alert

HeartLogic™ Heart Failure Index

HeartLogic™ Includes:

a. Composite HeartLogic™ Index trend
b. Actionable HeartLogic™ Alert
c. Configurable HeartLogic™ Threshold
d. Heart Failure Management Report with HeartLogic™ Data

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Heart Sounds were traditionally evaluated based on physician audibility using a stethoscope.

- In a normal subject, the first heart sound S1 happens shortly after the Q-wave in an EKG, produced by the closing of atrioventricular valves.
- S3 is caused by rapid filling of blood against a stiffer ventricular wall during passing filling. It may not be audible in normal subject.
Heart sounds are measured from the accelerometer and reveals signs of elevated filling pressure and weakened ventricular contraction via S3 and S1 heart sounds.

Worsening heart failure may be associated with an increase in S3 or a decrease in S1, or both.
Device-measured S3 more efficient than auscultation

Device-based S3 includes audible and sub-audible frequencies and therefore can pick up vibrations that cannot be detected by the human ear.

- Device-based S3 was significantly louder in patients with HF events
- Auscultated S3 was mostly absent and no different between groups


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Device-based S1 and S3 measured during clinically stable periods

S3 and S1 amplitudes were **significantly different** in pre-event windows from those during clinically stable periods in ambulatory heart failure patients

A clinically stable period is defined as a period between office visits when: a) NYHA classification was unchanged, b) Weight change ≤ 5 lbs (2.27kg), c) No adverse events were reported between the visits
Device-measured 3S HFE prediction Vs. auscultated third heart sound

Device-measured S3 has better correlation with the risk of heart failure events over one year than auscultated S3

This superiority may be attributable to the subjective nature of auscultation, limitations of the frequency range of human hearing, as well as limitations of a single snap-shot auscultation assessment.
Device-measured S3 significantly correlated to echo parameters

In PRE-SENSE, a related feasibility study conducted on CRT-D patients:

- S3 amplitude was significantly correlated with EDT, EDR, E/A ratio and E/E’ ratio, which are often used to assess LV diastolic function.

- There was significant separation across almost all echo parameters between the low and high S3 groups (high = top quartile).

<table>
<thead>
<tr>
<th>Measures</th>
<th>Low S3 (n=48)</th>
<th>High S3 (n=14)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LVEF (%)</strong></td>
<td>41.5</td>
<td>28.4</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>LV Volume</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEDD (cm)</td>
<td>5.57</td>
<td>6.71</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEDV (mL)</td>
<td>134.8</td>
<td>182.6</td>
<td>0.005</td>
</tr>
<tr>
<td>LVESD (cm)</td>
<td>4.35</td>
<td>5.81</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVESV (mL)</td>
<td>83.5</td>
<td>134.6</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>LA volume</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAEDV (mL)</td>
<td>72.1</td>
<td>101.1</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>Diastolic Filling (E and A waves)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E (cm/s)</td>
<td>62.8</td>
<td>89.0</td>
<td>0.006</td>
</tr>
<tr>
<td>EDT (ms)</td>
<td>279.5</td>
<td>193.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EDR (m/s^2)</td>
<td>2.63</td>
<td>5.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>0.89</td>
<td>1.49</td>
<td>0.020</td>
</tr>
<tr>
<td>E/E’ septal ratio</td>
<td>13.2</td>
<td>19.4</td>
<td>0.003</td>
</tr>
<tr>
<td>E’ septal (cm/s)</td>
<td>5.31</td>
<td>4.29</td>
<td>0.162</td>
</tr>
</tbody>
</table>


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HeartLogic Sensors

Overview
- Heart Sounds
- Respiration
- Night Heart Rate
- Activity
- Thoracic Impedance
- Report

HeartLogic™ MultiSENSE Study Case Studies

- The Respiratory Sensor uses transthoracic impedance measurements to collect respiration-related data, specifically respiration rate and tidal volume.
- Respiration rate and tidal volume are combined to produce additional respiration metrics.
- **Worsening heart failure may be associated with an elevated RR, an increase in RR, or an increase in day-to-day RR variability.**

![Graph showing respiratory rate changes](image)

**MultiSENSE data; 6 months shown**

1. Respiratory rate **increases** prior to heart failure events.¹
2. Respiratory rate **above 20 breaths/min** on average over 30 days has **3.5-fold increased risk** of HF hospitalisation within the following 30 days.²
3. Respiratory rate with a **higher range** over 30 days has **4.9-fold increased risk** of HF hospitalisation within the following 30 days.³

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HeartLogic™
Heart Failure Diagnostic

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**Worsening heart failure** may be associated with **increases in Night Heart Rate**

**Night Heart Rate**

- Average Heart Rate from 12 am to 6 am
- Tends to capture close to resting heart rate for most patients
- Resting HR are known to be prognostic for cardiovascular outcomes
- Look for increases as a sign of heart failure worsening
Worsening heart failure may be associated with a decrease in a patient's activity level.

**Activity**

- Numbers of hours per day a patient is active.
- Overall status and fatigue.
HeartLogic Sensors

Thoracic Impedance

- The Thoracic Impedance sensor measures impedance between electrodes on the RV lead and the pulse generator (PG) can.
- Thoracic Impedance may be associated with the fluid level in the patient’s chest and may track fluid level changes.

Worsening heart failure may cause a patient’s fluid level to increase, therefore, decrease in thoracic impedance. This information can be valuable when used in conjunction with a multifactorial approach to assess and treat HF patients.

HeartLogic collects information through the implanted device without patient involvement and provides data via LATITUDE NXT 24/7.

HeartLogic™ Includes:

- **a** Composite
  HeartLogic™ Index trend

- **b** Actionable
  HeartLogic™ Alert

- **c** Configurable
  HeartLogic™ Threshold

- **d** Heart Failure Management Report with HeartLogic™ Data

High performing composite indicator for detecting worsening of heart failure using multiple physiologic measurements.

Enabling HeartLogic™: Quick review

There are essentially two steps required to enable HeartLogic:

- **Program the device** to ensure that Heart Failure Sensor Suite is activated. Heart Failure Sensor Suite is on by default.

- **Ensure that the patient with the implanted device is added to the Latitude™ NXT system, provided with a Communicator, and that the Latitude™ NXT system is programmed appropriately.**

It will take **up to 37 days** from the time of implant to the point where it begins compiling Index numbers, allowing potential transmission of HeartLogic™ Alerts over Latitude™ NXT, assuming it is programmed ON.

*In order to see HeartLogic data, remember that patients need to be on Latitude™ NXT and HeartLogic has to be activated for the patient.*
Primary Results from the MultiSENSE Study

A Multi-Sensor Algorithm Predicts Heart Failure Events in Patients with Implanted Devices

- International, multi-center, non-randomized, clinical study designed to develop and prospectively evaluate a multi-sensor index and alert for the early detection of worsening heart failure.
- New sensors created with enhanced components and novel data collection and processing techniques.

Key inclusion criteria
- HeartLogic Age 18 or above
- Currently implanted with a COGNIS CRT-D system
- NYHA Class II, III or IV within the last 6 months

Key exclusion criteria
- Documented as pacemaker dependent
- History of appropriate Tachy therapy 1 week prior to enrollment
- Likely to undergo lead or PG revision
- Subjects that have received a heart or lung transplant
- Receiving mechanical circulatory transplant
- A life expectancy of less than 12 months

Primary Results from the MultiSENSE Study

Independent clinical events committee (CEC) Adjudication:

<table>
<thead>
<tr>
<th>Heart failure Events (HFE)</th>
<th>Primary cause of event was worsening heart failure and</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Is <strong>admitted</strong> for HF and receives an augmented HF regimen with oral or intravenous medications, or</td>
</tr>
<tr>
<td></td>
<td>• Receives unscheduled <strong>intravenous</strong> decongestive therapy that does not involve formal in-patient hospital admission, regardless of the setting</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>True Position Alerts</th>
<th>• Onset before a usable HFEs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Recovery no earlier than <strong>30 days</strong> before usable HFEs</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HF Related Alerts</th>
<th>Same onset and recovery window but broader set of HF events:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• hospitalizations with a <strong>secondary</strong> cause of HF,</td>
</tr>
<tr>
<td></td>
<td>• outpatient visits with a primary cause of HF and augmented <strong>oral</strong> medication changes,</td>
</tr>
<tr>
<td></td>
<td>• HFEs that did not meet sensor <strong>data availability</strong> criteria or occurred within 45 days of device conversion</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Unexplained Alerts</th>
<th>• All other alerts</th>
</tr>
</thead>
</table>

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Primary Results from the MultiSENSE Study

Data was used to develop individual physiologic sensor trends and a multi-sensor composite alert for worsening heart failure.
Primary Results from the MultiSENSE Study

Overview
HeartLogic™ MultiSENSE Study
Case Studies

- **Endpoint 1:** Sensitivity for detecting usable heart failure events >40%
- **Endpoint 2:** Unexplained alert rate (UAR) per patient year <2.0
- **HeartLogic threshold** is configurable to user’s preference for sensitivity and specificity
- By increasing sensitivity the UAR decreases

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The MultiSENSE Study data validated that HeartLogic™:

- Had **high sensitivity** of 70% in detecting heart failure events

- Had a very **low burden** of less than 2 alerts per patient per year

- May have allow several **weeks of advanced notice** to clinicians of a potential event
HeartLogic™ Index Trends

MultiSENSE Study results showed that it could have allowed weeks of advanced notice to clinicians to a potential heart failure event.

Compared to 3 month baseline, HeartLogic Index was statistically higher beginning 29 days prior to event.

HeartLogic™ Index in patients with Heart Failure Events

HeartLogic™ Index in patients without Heart Failure Events

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Event Rate Ratio Presented as a LBCT at ESC-HF 2017

- At nominal HeartLogic Threshold = 16
  - HF Event Rate was **10x higher** when **IN** a HeartLogic Alert versus **NOT** in an alert
- 17 % of patient-days IN Alert State
HeartLogic was better pronosticator than a baseline NT-proBNP.

Overview

HeartLogic™ MultiSENSE Study

Event Rates as a Function of Daily HeartLogic Score

Event Rates as a Function of Baseline NT-proBNP
HeartLogic Significantly Augments The Prognostic Ability Of NT-proBNP Assessment

Overview
HeartLogic™
MultiSENSE Study
Case Studies

Half of patient follow-up in lowest risk group.

Event Rate Ratio compared to lowest risk group:

- LOW NT-proBNP, IN HL alert: 23.5
- HIGH NT-proBNP, OUT HL alert: 8.0
- HIGH NT-proBNP, IN HL alert: 50.0
Conclusions

• HeartLogic was established and validated in the MultiSENSE trial with a **sensitivity of 70% and UAR of 1.47 alerts / patient-year at the nominal value of 16**
  • Other HeartLogic values can be tailored to the user’s preference for sensitivity and specificity.

• **HeartLogic predicted risk** of HF event independent of baseline variables.

• Using HeartLogic threshold at 16, the median of detection was **34 days prior to a HFE**.
  • 89 % of true positive alerts occurred at least 2-weeks prior to a HFE.

• **Event Rate** was **10 times higher** when HeartLogic was **IN alert state** compared to **OUT of alert state**.

• Healthcare resources may be diverted to those with greater need.

• HeartLogic was a **better prognosticator than a baseline NT-proBNP**.
HeartLogic™ shifts heart failure patient management from reactive treatment to **proactive care** that is validated in the MultiSENSE Study to have:

- **High sensitivity** of 70% for detecting heart failure events
- **Weeks of advance notice** of a potential heart failure event
- **Low burden** of less than 2 alerts per patient per year

HeartLogic™ incorporates multiple sensors with a single composite alert:

- **Heart Sounds** (S1 & S3)
- **Impedance** (Thoracic)
- **Respiration** (Rate & Volume)
- **Activity** (Time Spent Active)
- **Heart Rate** (Night)

*HeartLogic™ shifts heart failure patient management from reactive treatment to proactive care that is validated in the MultiSENSE Study to have:

- High sensitivity of 70% for detecting heart failure events
- Weeks of advance notice of a potential heart failure event
- Low burden of less than 2 alerts per patient per year*