Application of digital technologies to enable neonatal digital biomarker discovery and clinical trials

An Opportunity and a Challenge
I serve as Head of Research and Chief Medical Officer for Philips North America

Philips is a global manufacturer of Medical Devices and Informatics Solutions
Outline

• Large-scale high resolution public data sets

• The need for a large-scale publicly available multiparameter neonatal DB

• Building high resolution data sets for neonatal research

• Leveraging large scale data to develop Digital Biomarkers
The MIT/Philips/Beth Israel Deaconess
Biomedical Research Partnership

- Research Groups
  - BIDMC – Critical Care
  - MIT
    - Clinical Decision Making - Computer Science and AI Laboratory – Prof Peter Szolovits
    - Laboratory of Computational Physiology – Prof Roger Mark
    - Research Laboratory of Electronics – Prof George Verghese
  - Philips HealthCare
    - Philips Research North America – Joe Frassica, MD/Brian Gross/Minnan Xu

- The project is funded by grants from the National Institute of Biomedical Imaging and Bioengineering (NIBIB) of the National Institutes of Health (NIH) under award numbers R01-EB001659 (2003-2013) and R01-EB017205 (2014-2018).
MIMIC III

- 58,000 hospital admissions for
  - 38,645 adults
  - 7,875 neonates

- Clinical DB
  - 40426 ICU Admissions

- Waveform DB
  - 67830 Waveform Records (30,000 ICU patients)
    - ECG, ABP, Respiration, SpO2, Numerics – aperiodic measurements and semi continuous measures

- Waveform DB Matched Subset
  - 22,317 waveform records
  - 22,247 numeric records,
  - 10282 Time matched waveform and Clinical DB Records

https://mimic.mit.edu
eRI Institute Db

- 4+ Million ICU Admissions
- 200 Hospitals
  - Allergies
  - History
  - Diagnoses
  - Vital signs – (5 minute median values)
  - Medications
  - Laboratory values
  - Microbiology
  - Treatments
  - APACHE Scores
  - Nurse Charting
eICU Collaborative Research Db

- Philips/MIT Collaboration
- de-identified health data from
  - > over 200,000 critical care admissions
  - 200 U.S. Hospitals
  - 2014–2015
- Data
  - Allergies
  - History
  - Diagnoses
  - Vital signs – (5 minute median values)
  - Medications
  - Laboratory values
  - Microbiology
  - Treatments
  - APACHE Scores
  - Nurse Charting

https://eicu-crd.mit.edu
MIMIC III Database

- **Hospital**
  - **ICU**
    - MICU
    - SICU
    - CCU
    - CSRU
    - NICU
  - **Bedside monitoring**
    - Vital signs
    - Waveforms
    - Trends
    - Alarms
  - **Chart**
    - Fluids
    - Medications
    - Progress notes
- **Tests**
  - Laboratory
  - Microbiology
- **Orders**
  - Provider order entry (POE)
- **Billing**
  - ICD9
  - DRG
  - Procedures (CPT)
- **Demographics**
  - Admission/discharge dates
  - Date of birth/death
  - Religion/ethnicity/marital status
- **Notes and reports**
  - Discharge summaries
  - Radiology (X-ray, CT, MRI, Ultrasound)
  - Cardiology (ECHOCG, ECG)
- **External**
  - Social Security Death Index

**MIMIC-II Database**

- Calculated variables (SAPS, SOFA, Elixhauser co-morbidity)
- De-identification
- Date shifting
- Format conversion
- User feedback and corrections
Data is the lifeblood of AI and biomarker research and there is a shortage of available pediatric and neonatal data.
## Available pediatric high resolution data sets

<table>
<thead>
<tr>
<th>DataBase</th>
<th>Resolution</th>
<th>Hospitals</th>
<th>Size</th>
<th>Accessibility/Cost</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virtual PICU systems (VPS)</td>
<td>High</td>
<td>119</td>
<td>600,000</td>
<td>Moderate/free to VPS members (Fee required)</td>
<td>Use by non-members requires partnership with a member hospital investigator. Requires review by the Research Committee, which is primarily intended to ensure that multiple investigators are not attempting to answer the same question.</td>
</tr>
<tr>
<td>ANZPIC registry</td>
<td>High</td>
<td>24</td>
<td></td>
<td>Moderate/free</td>
<td>Australia and New Zealand</td>
</tr>
<tr>
<td>PICANet registry</td>
<td>High</td>
<td>32 Uk and Ireland</td>
<td></td>
<td>High/free</td>
<td>Uk and Ireland</td>
</tr>
<tr>
<td>STS congenital database</td>
<td>High</td>
<td></td>
<td></td>
<td>Moderate/low</td>
<td>Congenital Cardiac Surgery patients</td>
</tr>
</tbody>
</table>

A multiparameter federated DB for neonatal research
The need for a publicly available resource

– Neonatal data is rare (relatively)
– Multi-center data is a stronger basis for creating conclusions
– Active data collection is costly and difficult to maintain
– Centers tend to treat data as proprietary
– Local treatment practices can bias machine learning findings
– Small populations may bias findings
A multiparameter federated DB for neonatal research
The case for a publicly available resource

– A large-scale publicly available DB for application of machine learning and clinical trials to neonatal medicine
– Registries are limited to narrowly defined data sets
– Data need to be collected passively to create sustainability
– Functions as baseline data collection for clinical trials
– Additional parameters necessary for a particular trial can easily be added to base data set
– No need to re-invent data collection for each trial
Creating large-scale multiparameter databases
Waveform data collection
Waveform Data Warehouse Overview

- DWC captures patient monitoring:
  - Patient ADT/Demographics
  - Waveforms
  - Numeric parameters
  - Alarms and alerts
  - Arrhythmia analysis from the monitoring system

- Data is stored in an open relational SQL database with built-in SQL stored procedures for data extraction (institution has complete data access and ownership) – ON SITE

- DWC data storage requirements approx."
  ~1 GB/Patient/Day (adult hospital average); peds: ~350-500 MB/pat/day
  Example: 75 pediatric patients std waves ~10 TB/yr
  w/ 500sps ECG ~14 TB / year
DWC Web-based browser: 4 context-linked components

Demographics:

Waveforms:

Numeric Vital Sign Parameters:

Alarms and Technical Alerts:
Creating large-scale multiparameter databases

A knowledge, data normalization, integration and calculations platform and federated multiparameter DB
A knowledge, data normalization, integration and calculations platform and federated multiparameter DB
Normalized - mapped data created at the source

Site Profile

Clinical Analytics
Intellibridge Enterprise

Philips Clinical Analytics Platform
Hosted by HealthSuite
Digital Platform, locally, or enclave

Electronic Clinical Data Interfaces
- ADT
- Lab
- Orders
- F&A
- I&O
- Rad
- Docs
- MAR
- Device
- User defined

Other Data

Data Stager

On Premise

Remote/Enclave/On Premise

Cloud In Endpoint
Interface Routes
Data Warehouse

Cloud out Endpoint
Interface Routes

User entered data

App Specific Mapper

Re-Identify

Premise In Endpoint

Precise Out Endpoint

Dec-Identify

Staging/Filtering

Nomenc
Isture Coding

HI7. ORY, XML, WS File
Pediatric Digital Biomarker Discovery and Predictive Algorithm Development
Our approach: we use multimodal data and machine learning for phenotyping, knowledge discovery, and risk stratification

Applications
- Hemodynamic instability indicator
- Early deterioration index
- Acute kidney injury
- Noninvasive blood gas estimation
- Discharge readiness

Clinical domain knowledge
Multimodal integration and feature extraction
Machine learning for healthcare

Longitudinal data including home and primary care
How we acquire multimodal data from a partner hospital with large scale de-identification architecture
Pediatric Hemodynamic Instability
Pedi-HII
Algorithm to predict hemodynamic instability in the pediatric ICU

Unmet need
• Pediatric physiology requires customized digital biomarkers and algorithm.

Solution
• Data mining of pediatric ICU databases.
• Predictive algorithm handles different age groups, from a few months to 17 years old.
Algorithm to predict hemodynamic instability in the pediatric ICU

Data:

Goal:
- Predict the need for hemodynamic interventions for patients already in the PICU
  - **Bolus fluid** (colloid or crystalloid) > 10 ml/kg/hour
  - **Initiation of vasoactive medications** (dopamine, epinephrine, norepinephrine, neosynephrine, vasopressin)

Table 2: Summary statistics stratified by exposure and control groups.

<table>
<thead>
<tr>
<th></th>
<th>All observations</th>
<th>Exposure group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean age (years)</strong></td>
<td>N = 7052 (970)</td>
<td>N = 2945 (235)</td>
<td>N = 4107 (735)</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>6.9 (4.3)</td>
<td>6.6 (3.9)</td>
<td>7.1 (4.4)</td>
</tr>
<tr>
<td>Mechanically ventilated (%)</td>
<td>39.3 (66.2)</td>
<td>56.1 (85.9)</td>
<td>28.5 (60.4)</td>
</tr>
<tr>
<td>Mean PICU LOS (days)</td>
<td>8.2 (6.6)</td>
<td>15.3 (13.5)</td>
<td>3.6 (4.6)</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>3 (4.2)</td>
<td>6 (14.9)</td>
<td>1.1 (1.1)</td>
</tr>
</tbody>
</table>

Values in parentheses correspond to the validation dataset
LOS length of stay, PICU pediatric intensive care unit

- CHLA: 42% instability
- St.Mary’s: 24% instability
Algorithm to predict hemodynamic instability in the pediatric ICU

- Bold variables selected as being predictive out of a total of 36 variables.
- We learned age-dependent risk thresholds for each variable.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Features (units of measurement and percentage of patients with that feature recorded) for training (and validation) datasets.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial blood gas</td>
<td>Invasive vitalss</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>63 (92)</td>
</tr>
<tr>
<td>Bicarbonate (HCO₃⁻)</td>
<td>mEq</td>
</tr>
<tr>
<td>Arterial PaCO₂</td>
<td>mmHg</td>
</tr>
<tr>
<td>SaO₂</td>
<td>%</td>
</tr>
<tr>
<td>Arterial base excess (aBE)</td>
<td>mEq/L</td>
</tr>
<tr>
<td>Arterial PaO₂</td>
<td>mmHg</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventilator parameters</td>
<td>Noninvasive vitals/demographics</td>
</tr>
<tr>
<td>pH ratio</td>
<td>41 (26)</td>
</tr>
<tr>
<td>FiO₂</td>
<td>%</td>
</tr>
<tr>
<td>Mean airway pressure</td>
<td>cmH₂O</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heart rate (HR)</td>
</tr>
<tr>
<td></td>
<td>Respiratory rate (RR)</td>
</tr>
<tr>
<td></td>
<td>SpO₂</td>
</tr>
<tr>
<td></td>
<td>Age</td>
</tr>
<tr>
<td></td>
<td>Temperature (T)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Basic metabolic panel</td>
<td>Comprehensive metabolic panel</td>
</tr>
<tr>
<td>Glucose</td>
<td>mg/dl</td>
</tr>
<tr>
<td>Chloride</td>
<td>mEq/L</td>
</tr>
<tr>
<td>Blood urea nitrogen (BUN)</td>
<td>mg/dl</td>
</tr>
<tr>
<td>Creatinine</td>
<td>mg/dl</td>
</tr>
<tr>
<td>Potassium</td>
<td>mEq/L</td>
</tr>
<tr>
<td>Sodium</td>
<td>mEq/L</td>
</tr>
<tr>
<td>Complete blood count</td>
<td></td>
</tr>
<tr>
<td>WBC – leukocytes</td>
<td>K/µl</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>g/dl</td>
</tr>
<tr>
<td>Additional tests</td>
<td></td>
</tr>
<tr>
<td>Magnesium</td>
<td>mg/dl</td>
</tr>
<tr>
<td>Lactic acid</td>
<td>mg/dl</td>
</tr>
</tbody>
</table>

All 36 features were input to the AdaBoost-ABM classifier to classify hemodynamic instability. Among the 36 features, only 21 (highlighted in bold) were selected by the model.

RBC red blood cells, WBC white blood cells
Algorithm to predict hemodynamic instability in the pediatric ICU

Algorithm performance

• At one hour before physicians give intervention, we can classify unstable patients with AUC of 0.8.

• Multiparameter data driven risk assessment using labs, and vitals outperform traditional vitals only assessment using blood pressure and shock index.

• Algorithm performed similarly for different age groups.

Table 3

<table>
<thead>
<tr>
<th>Age group</th>
<th>N*</th>
<th>AUROC#</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–12 months</td>
<td>165/300</td>
<td>0.82/0.78</td>
</tr>
<tr>
<td>1–3 years</td>
<td>90/245</td>
<td>0.77/0.82</td>
</tr>
<tr>
<td>3–6 years</td>
<td>94/147</td>
<td>0.82/0.72</td>
</tr>
<tr>
<td>6–12 years</td>
<td>151/159</td>
<td>0.74/0.89</td>
</tr>
<tr>
<td>12–20 years</td>
<td>191/105</td>
<td>0.75/0.85</td>
</tr>
</tbody>
</table>

*Number of patients for that particular age group (training/validation)
#Reported at the time of hemodynamic intervention (training/validation)
AUROC area under receiver operating characteristic curve
Comparison of adult and pediatric machine learning resources
Available data

<table>
<thead>
<tr>
<th>Database</th>
<th>DB Encounters</th>
<th>Patients</th>
<th>Hospitals</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIA -1 / HII - 2</td>
<td>MIMIC II</td>
<td>40000+</td>
<td>22020</td>
</tr>
<tr>
<td>eRI Db</td>
<td>4+ M</td>
<td>41707</td>
<td>200+</td>
</tr>
<tr>
<td>Pedi HII</td>
<td>CHLA</td>
<td>31583</td>
<td>7052</td>
</tr>
<tr>
<td>St Mary’s</td>
<td>2435</td>
<td>970</td>
<td>1</td>
</tr>
<tr>
<td>Pedi EDI</td>
<td>CTH</td>
<td>15447</td>
<td>15447</td>
</tr>
</tbody>
</table>
Our Pediatric Biomarkers Team

- Minnan Xu, PhD
- Junzi Dong, PhD
- Cristhian Potes, PhD
- Jonathan Rubin, PhD
- Asif Rahman, PhD
- Bryan Conroy, PhD
- Joe Frassica, MD

- Major Collaborators
  - Kit Newth, MD (CHLA),
  - David Inwald, MD (St Mary’s)