Development of Novel Digital Clinical Endpoints and a Global Standard of Measures for Application in Sensor Based Assessment of Mobility and Balance

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Clinical Research and Development

Investing in Digital Innovation and Transformation

"Software is changing how clinicians practice medicine, how consumers manage their own health and how patients and providers interact."

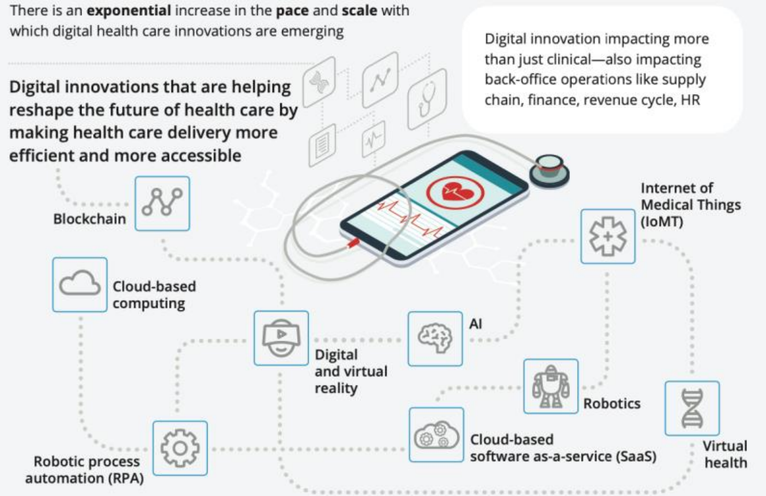
Deloitte

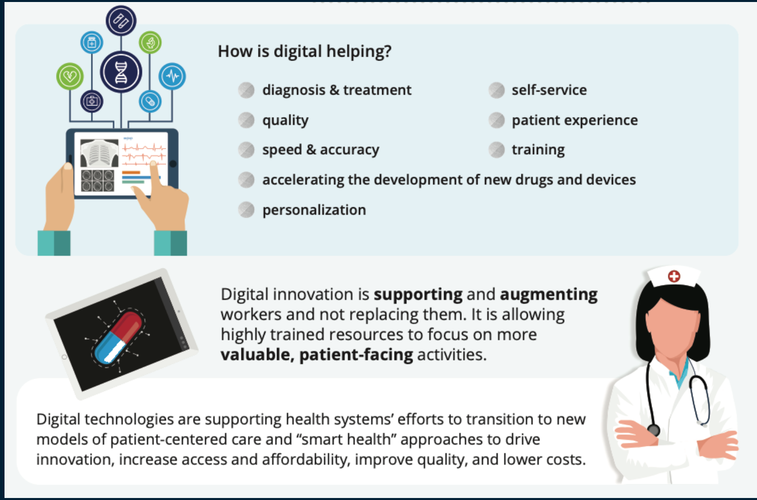
One revolutionary development in digital health technology is software that can perform complex medical functions—**Software as a Medical Device.**

Software that can diagnose conditions, suggest treatments, and inform clinical management

Global Health Outlook

Digital Innovation and Transformation

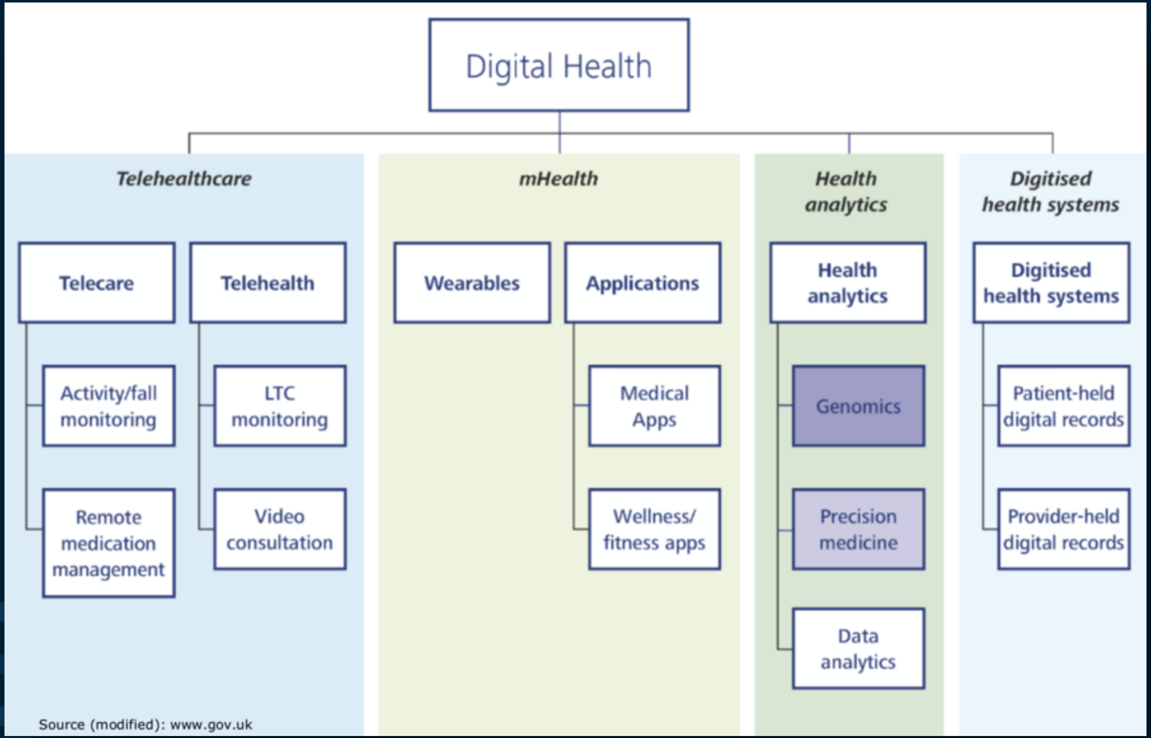




Deloitte.

European Medicines Agency

Digital Health



EMA Experience with review of Digital Technology proposals in Medicine Development Programs

U.S. Food and Drug Administration

Digital Health

- Many medical devices now have the ability to connect to and communicate with other devices or systems.
- Devices that are already FDA approved or cleared are being updated to add digital Features.
- New types of devices that already have these capabilities are being explored.

Many stakeholders are involved in digital health activities, including patients, health care practitioners, researchers, traditional medical device industry firms, and firms new to FDA regulatory requirements, such as mobile application developers

- Wireless Medical Devices
- Mobile medical apps
- Health IT
- Telemedicine
- Medical Device Data Systems
- Medical device Interoperability
- **Software as a Medical Device (SaMD)**
- General Wellness
- Cybersecurity

FDA U.S. FOOD & DRUG ADMINISTRATION

Mobilize-D

Connecting Digital Mobility Assessment to Clinical Outcomes for Regulatory and Clinical Endorsement

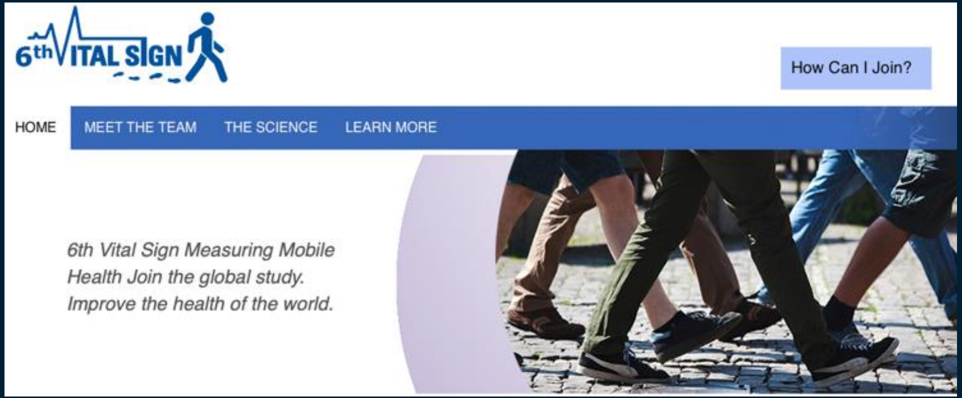
Mobilise-D will build an all-encompassing, clinically-valid digital mobility assessment system capable of use across all conditions where mobility loss is relevant and bring with it a personalized approach to healthcare for the benefit of citizens in the EU and globally

Our ultimate goal is to provide a validated, robust set of algorithms to measure digital mobility outcomes and in turn, inform therapeutic development, clinical practice, precision medicine, industrial development and stakeholder approval.”

Professor Lynn Rochester

6th Vital Sign

Duke Clinical Research Institute



Research Trends

“Sensors for Gait, Human Movement Analysis and Health Monitoring”

sensors

an Open Access Journal by MDPI

Sensors for Gait, Human Movement Analysis, and Health Monitoring

Guest Editor:

Dr. Marco Iosa
IRCCS Foundation Santa Lucia, Laboratory for the Study of Mind and Action in Rehabilitation Technologies, Italy

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Deadline for manuscript submissions:
31 December 2020

Message from the Guest Editor

This Special Issue aims to highlight the most recent research regarding sensors and their applications in gait analysis and, more generally, human movement analysis, including in health monitoring.

Contributions are invited from groups active in this field of research.

- gait analysis
- locomotion
- movement assessment
- motion capture
- stereophotogrammetry
- inertial measurement unit
- health monitoring

Motion Sensors

In Silico Digital Twins

SCIENTIFIC REPORTS
naturereseach

Estimating wearable motion sensor performance from personal biomechanical models and sensor data synthesis

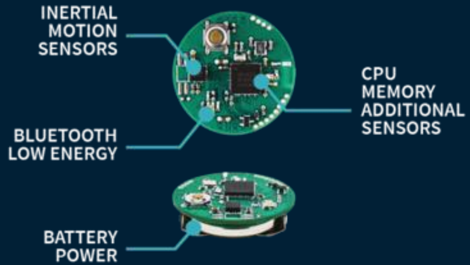
Oliver Amft and Adrian Derungs

Digital Health, Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU), Erlangen, 91052, Germany

Derungs, A., Amft, O. Estimating wearable motion sensor performance from personal biomechanical models and sensor data synthesis. *Sci Rep* **10,** 11450 (2020). https://doi.org/10.1038/s41598-020-68225-6

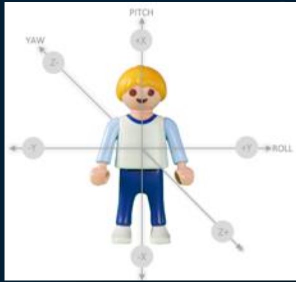
Materials

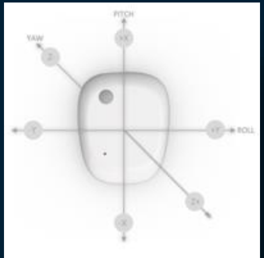
Inertial Measurement Unit



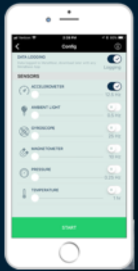
mbientlab MMR
9-axis IMU Fusion Sensor

The MetaMotionR (MMR) is a wearable device that offers real-time and continuous monitoring of motion and environmental sensor data.





mbientlab



MetaBase

Materials

Software

- SAS Viya Analytic Platform

https://www.sas.com/en_us/software/viya.html

- SAS Event Stream Processing

https://www.sas.com/en_us/software/event-stream-processing.html

- SAS Analytics for IoT

https://www.sas.com/en_us/software/analytics-iot.html

SAS Viya

Test Subjects

Fun Science Project for the Whole Family

Morbidity = Enthesitis[1]

- Subjects: females in their mid-teens
- Symptoms much worse in one twin
- Assessment was made without therapeutic intervention

Morbidity = Psoriatic Arthritis[2]

- Subject: Male in his mid 50's
- Assessment was made without therapeutic intervention

[1]*Enthesitis:* Tenderness at the site of attachment of bone to a tendon, ligament, or joint capsule
[2]*Psoriatic Arthritis*: Arthritis associated with psoriasis. The exacerbations and remissions of arthritic symptoms do not always parallel those of psoriasis

(Taber's Cyclopedic Medical Dictionary)

Assessment Protocol

Berg Balance Scale

Berg Balance Scale (BBS)

Item Description: SCORE (0–4)

_________ 1. Sitting to standing
_________ 2. Standing unsupported
_________ 3. Sitting unsupported
_________ 4. Standing to sitting
_________ 5. Transfers
_________ 6. Standing with eyes closed
_________ 7. Standing with feet together
_________ 8. Reaching forward with outstretched arm
_________ 9. Retrieving object from floor
_________ 10. Turning to look behind
_________ 11. Turning 360 degrees
_________ 12. Placing alternate foot on stool
_________ 13. Standing with one foot in front
_________ 14. Standing on one foot
_________ Total

Equipment needed:	Ruler, 2 standard chairs (one with arm rests, one without), footstool or step, stopwatch or wristwatch, 15 ft walkway
Time needed:	15–20 minutes
Scoring:	A five-point ordinal scale, ranging from 0–4. “0” indicates the lowest level of function and “4” the highest level of function. Total score = 28
Interpretation:	41–56 = low fall risk 21–40 = medium fall risk 0–20 = high fall risk <36 fall risk close to 100%

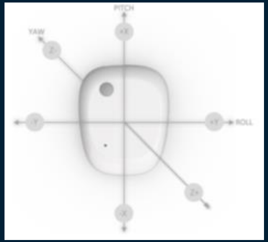
Subject Assessment

Recording Protocol

- IMU was placed at the base of the C7 vertebra
- Acceleration and Gyroscopic recordings were made
- Data were collected at a sample rate of 50 Hz
- Each recording lasted 30 seconds
- Recordings allowed an initial 5 second period for subject to stabilize

elapsed (s)	x-axis (g)	y-axis (g)	z-axis (g)	x-axis (deg/s)	y-axis (deg/s)	z-axis (deg/s)
0.00	-0.0086	-0.0002	-0.0099	-0.1070	0.6970	0.4150
0.02	-0.0096	0.0028	-0.0119	0.1710	0.5140	0.4650
0.04	-0.0096	0.0068	-0.0109	0.3770	0.3960	0.3770
0.06	-0.0136	-0.0022	-0.0099	0.3120	-0.1870	0.1370
0.08	-0.0076	-0.0022	-0.0049	0.3510	-0.4840	0.0380
0.10	-0.0016	-0.0002	-0.0029	0.5720	-0.7930	0.3050
0.12	-0.0006	0.0018	-0.0059	-0.1070	-1.8250	-0.3010
0.14	0.0014	0.0008	-0.0039	-0.1750	-1.7190	-0.2740
0.16	0.0014	0.0008	-0.0049	0.4540	-1.1890	0.2400
0.18	-0.0026	0.0028	-0.0039	0.4610	-0.9870	0.6900
0.20	-0.0006	0.0038	-0.0009	-0.1790	-0.4650	1.1200
0.22	0.0004	0.0008	0.0001	-0.2100	-0.3660	1.0180
0.24	0.0024	0.0008	-0.0009	-0.0910	-0.6210	0.8840
0.26	0.0024	0.0028	0.0011	-0.0230	-0.5180	1.0140
0.28	0.0004	-0.0002	-0.0029	0.2020	-0.1450	0.8120
0.30	0.0004	-0.0002	-0.0049	0.2520	0.3320	0.7280
0.32	-0.0006	0.0008	-0.0049	0.5180	0.4000	0.6360
0.34	-0.0046	0.0008	-0.0059	0.5600	0.0110	0.2710
0.36	-0.0036	0.0018	-0.0059	0.4190	0.4460	0.1600
0.38	-0.0036	0.0038	-0.0049	0.4650	0.7810	0.2520

- Acceleration was measured in units of gravitational force (g).
- Gyroscopic measurements of rotation were made in Degrees per Second (deg/s)



Test Subjects

Recording Protocol

- Four assessments were made for each subject in triplicate
  - Standing with eyes open
  - Standing with eyes closed
  - Standing with eyes open supported
  - Sanding with eyes closed supported

Data Preparation

Accelerometer Data

- 1st 5 seconds discarded to allow subject to settle into position
- Discarded initial 5 seconds of time series
- Retained following 20 seconds for analysis
- Aggregated accelerometer data
  - Z-normalized
  - By axial plane
  - Eyes open vs. closed
  - Standing supported vs. unsupported

Eyes Open: X axis (deg/s)

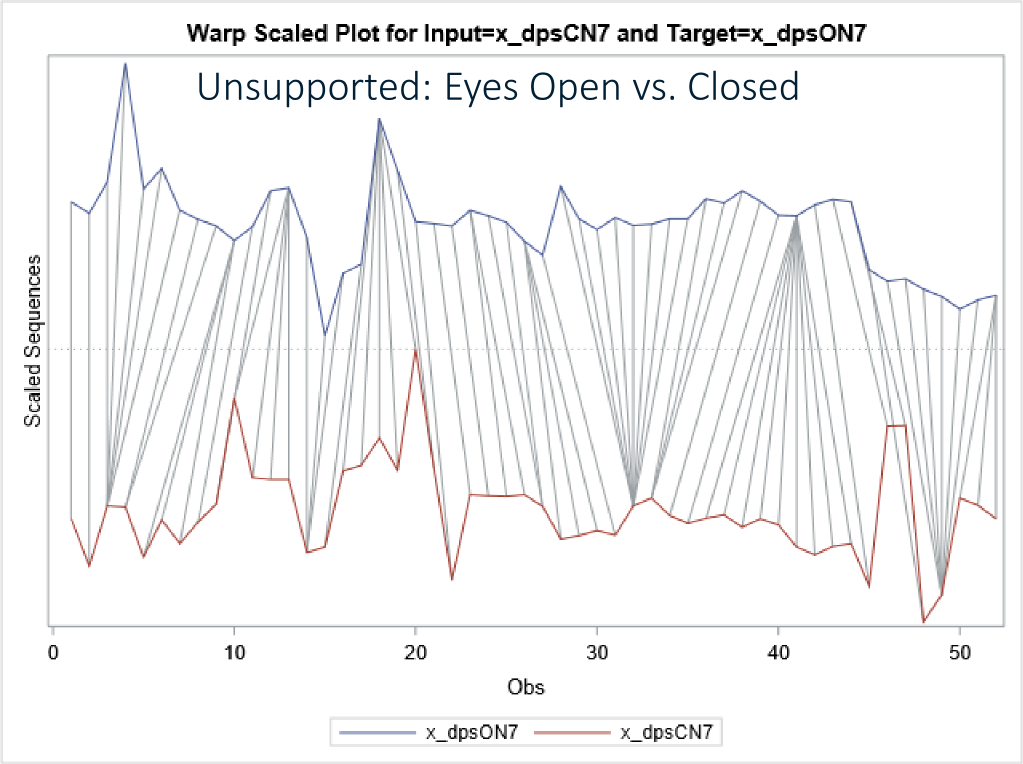
Seconds	Supported	Unsupported
5.02	0.305	0
5.04	0.152	-0.091
5.06	0.091	-0.122
5.08	0.213	-0.061
5.1	0.305	0
5.12	0.213	0.061
5.14	0.03	0.061
...	...	...

Data Analysis

Compared subject data using Dynamic Time Warping (DTW)

DTW is a method for assessing the similarity of 2 time series that may vary in timing

- PROC SIMILARITY
- Warp constraint = 10%
- Time Series Comparisons
  - Unsupported: Eyes Open/Closed
  - Supported: Eyes Open/Closed
  - Eyes Open: Unsupported/Supported
  - Eyes Closed: Unsupported/Supported



DATA Analysis

Subject Segmentation - Classification

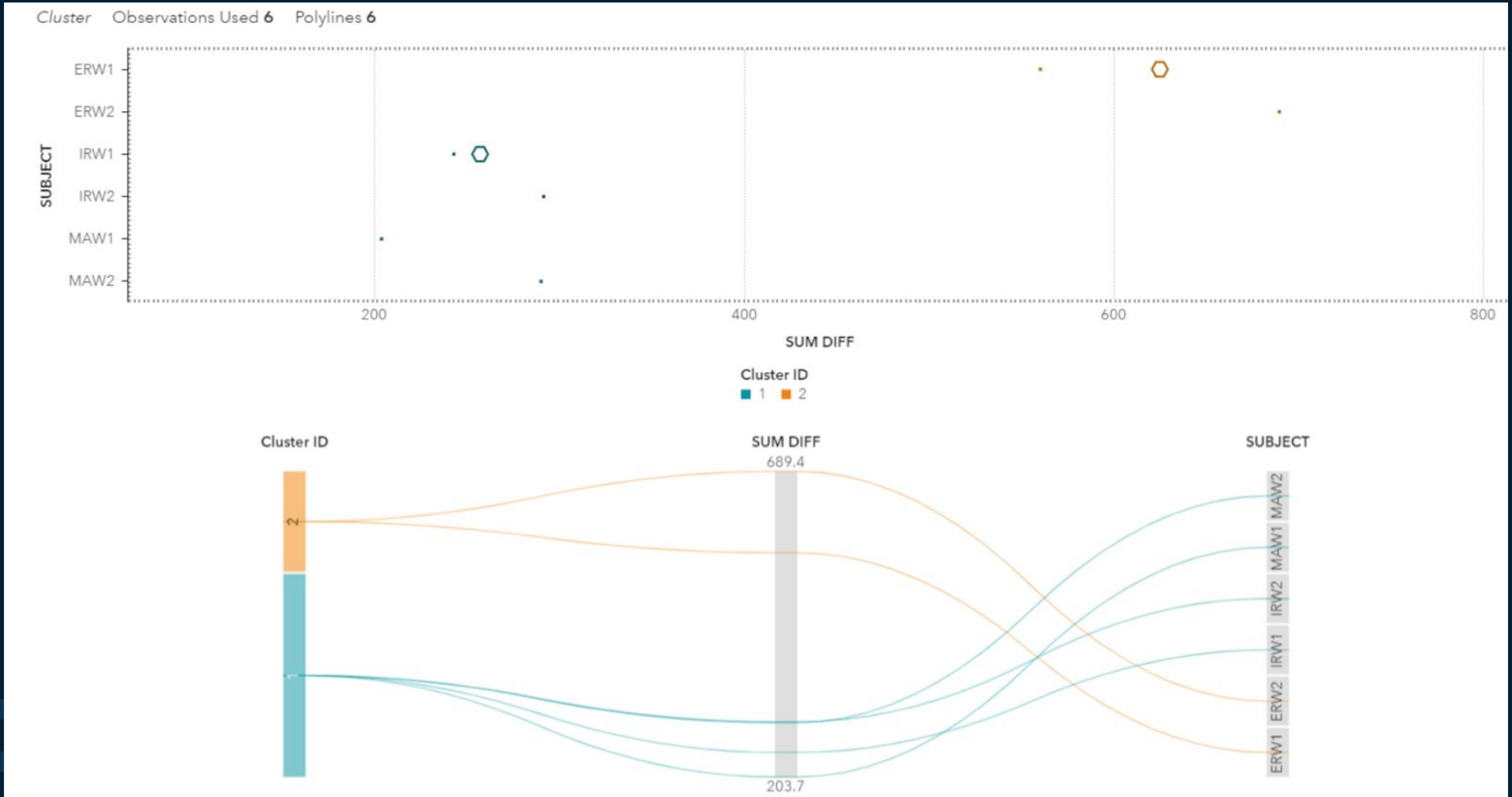
- Summed minimum (x, y, z) and maximum (x, y, z) relative path means from similarity analysis for each subject
- Difference between summed means used to compare subjects/replicates

Unsupported: Eyes Open vs. Closed		
REP	SUBJECT	SUM DIFF
1	ERW	599.0
2	ERW	862.9
1	IRW	198.1
2	IRW	122.8
1	MAW	372.6
2	MAW	321.4

Eyes Open: Supported vs. Unsupported		
REP	SUBJECT	SUM DIFF
1	ERW	560.1
2	ERW	689.4
1	IRW	242.8
2	IRW	291.4
1	MAW	203.7
2	MAW	290.0

Clustering Analysis

Unsupported – Eyes Open vs. Eyes Closed



DATA Analysis

Similarity Matrix: X Axis - Unsupported, Eyes Open

SUBJ/REP	ERW 2	ERW 1	IRW 2	IRW 1	MAW 2	MAW 1
ERW 2	0.0	124.5	1168.0	368.5	352.9	150.8
ERW 1	124.5	0.0	1137.5	349.2	256.9	121.0
IRW 2	1168.0	1137.5	0.0	864.6	1001.1	1157.3
IRW 1	368.5	349.2	864.6	0.0	271.8	256.3
MAW 2	352.9	256.9	1001.1	271.8	0.0	281.9
MAW 1	150.8	121.0	1157.3	256.3	281.9	0.0

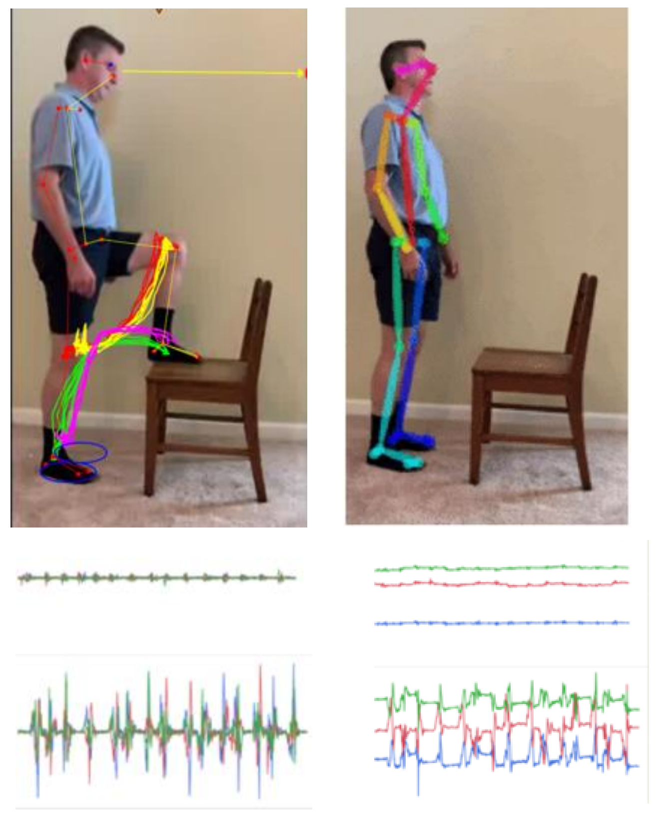
Discussion

Observations & Considerations for Future Study

- Supported baseline provides a nominal starting point for comparison
- Unsupported eyes open vs closed compares non-vestibular and vestibular balance
- Replicates demonstrate the results are reproducible
- Variance in pathophysiology and severity of medical conditions can be detected
- Adjusting support height (elbow bend) or developing a different method of support may result in a better nominal measure, thereby decreasing variability of within subject measurements

Digital Twin

Video Training and Sensor Data



Knee Up/Down Modeling
SAS Data Step for Scoring Data

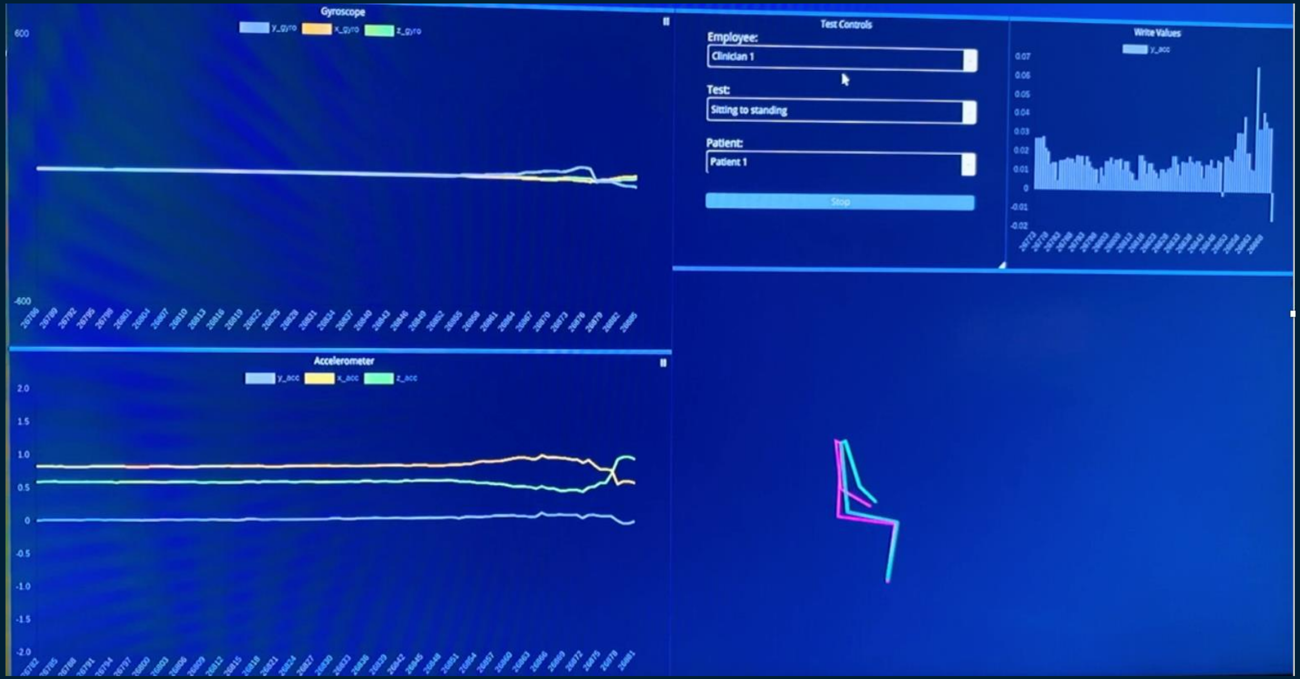
```
LABEL Prob_0= 'Predicted: TARGET=0';
LABEL Prob_1= 'Predicted: TARGET=1';


Prob_0=0;
Prob_1=0;
IF z_axis_g_>=0.441 THEN DO; Prob_0=Prob_0+0.00949809763486798;
Prob_1=Prob_1+0.990501902365132;
END;
ELSE DO;
 IF y_axis_g_>=0.08 THEN DO; Prob_0=Prob_0+0.0625819090296167;
Prob_1=Prob_1+0.937418090970383;
 END;
 ELSE DO; Prob_0=Prob_0+0.984192837130963; Prob_1=Prob_1+0.0158071628690365;
 END;
END;
```

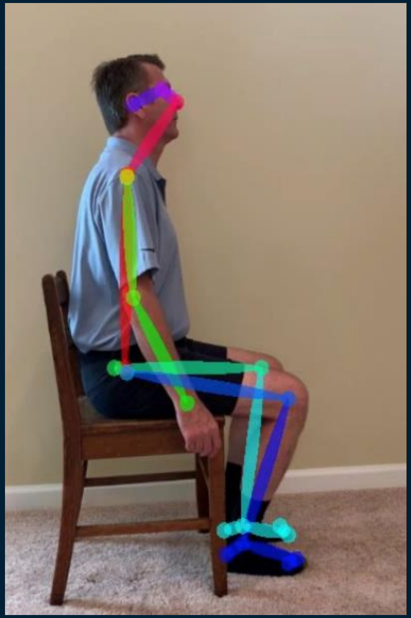
Knee Up/Down Modeling
Python Code for Scoring Data

```
from __future__ import division
import jmp_score as jmp
from math import *
import numpy as np

""" Python code generated by JMP v14.2.0 """

def getModelMetadata():
return {"creator": u"Partition", "modelName": u"", "predicted": u"TARGET", "table":
u"MAW_KNEE_TRAINING", "version": u"14.2.0", "timestamp": u"2019-09-05T02:20:29Z"}


def getInputMetadata():
   return {
      u"y-axis (g)": "float",
      u"z-axis (g)": "float"
}
```

Multimodal Assessment

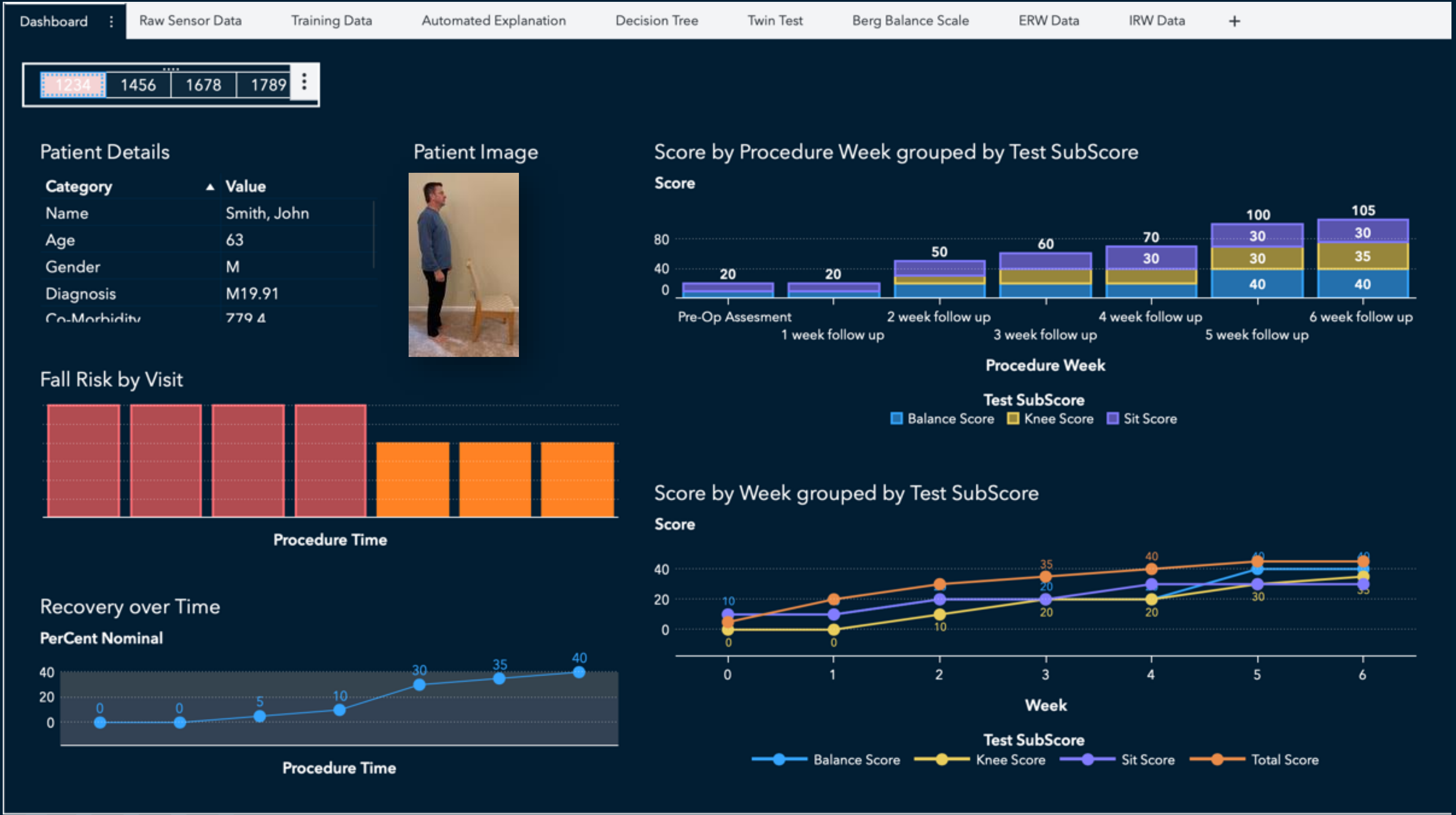
Digital Twin





Enabling Hybrid/Virtual Clinical Trials

Enabling Hybrid/Virtual Clinical Trials



Thank You!