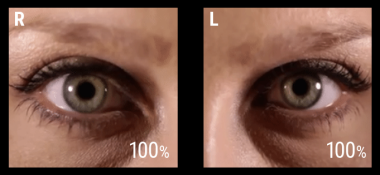
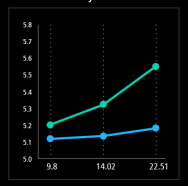
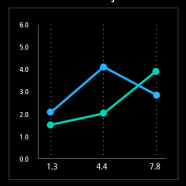
RESULTS: Normal

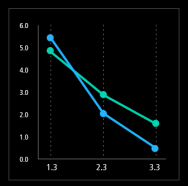


Dilation Velocity mm/s

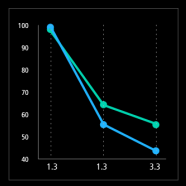


Constriction Velocity mm/s



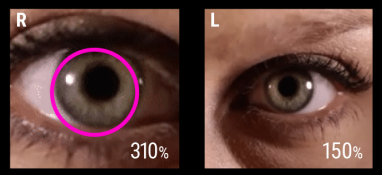


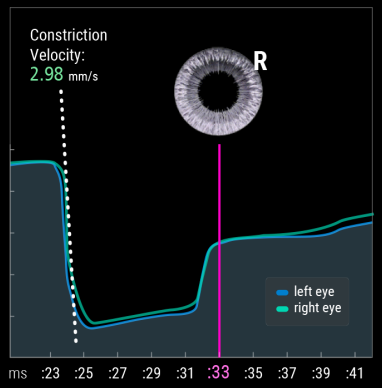
Constriction Amplitude mm



Constriction Percentage %

RESULTS: Normal

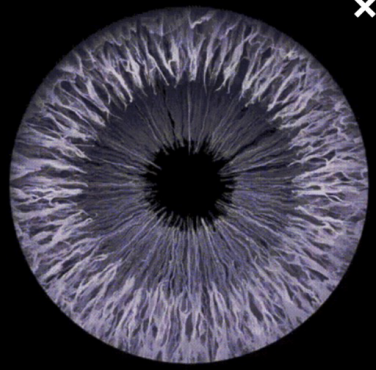


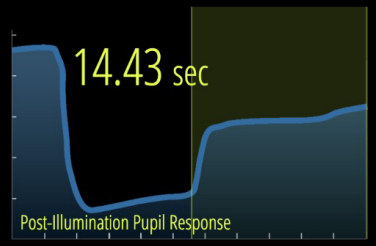


Pupil Latency: 0.71 mm

Constriction Velocity: 2.98 mm/s

Dilation Velocity: 9.03 mm/s



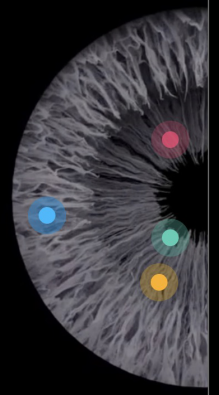


PIPR

Pupillary Escape

Presence of Narcotics

Low
12.3%
Stimulant



High
68.6%
Depressent

None
0.03%
Opiate

Low
12.3%
Hallucinogen

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PURPOSE OF THIS DOCUMENT

This Product Requirements Document (PRD) serves as master and roadmap. It provides the most comprehensive perspective of BioTrillion's overall Platform development effort and reflects BioTrillion's substantial research and discovery activities to date (6/2019), the entirety of which, though confidential, is available to key participants in the development process.

BIOTRILLION BACKGROUND

We spend less than 1% of our time in a Medical setting and expect the Medical data generated there to lead to enhanced outcomes. Medical data are abundant, but siloed, unstructured, and intermittent. Much is not yet adequately used to advance healthcare.

Medical settings offer access to tremendous medical experience and clinical diagnostics tools; however, their utility will be fundamentally limited if typical consumers only spend less than 1% of their total time in there. The Consumer advantage is access to the other 99% observable window —the life setting. However, there is a lack of novel continuous and objective solutions to digitally generate truly insightful measures expressed in life settings.

The body responds to diseases and drugs, via phenotypic "expressions" outside of a Medical setting and in the Life setting, as subtle physiologic and behavioral "biomarkable" signs. BioTrillion term these signs as LIFEdataTM. Biomarkers can be digitally measured using existing multimodal sensors embedded within consumer smart devices, through modalities such as optical, acoustic, kinetic, vitals, and others. Common consumer devices now provide the ability to evolve health measures from intermittently longitudinal to continuous, yielding computationally and statistically enhanced health analytics for disease detection and drug development.

Healthcare deployment and discovery has for centuries focused on post-symptomatic Intervention, when most diseases are developed, and largely responsible for the ballooning multi-trillion-dollar global economic healthcare burden. Recent innovative healthcare solutions have shifted to pre-disease Prevention, with a focus on general wellness and genetic prediction. This swing overlooks the promise of pre-symptomatic Detection, creating both a void and an opportunity to engage Consumers in the generation of continuous, convenient, affordable, and objective digital biomarkers to detect developing diseases and democratize drug development.

BioTrillion is developing BioEngine4D, a health technology platform, to serve Consumers worldwide by democratizing data-driven drug development and digitally detecting developing diseases early in the health-continuum. BioEngine4D proprietarily generates LIFEdata as novel digital biomarkers generated from common smartphone sensors and BioTrillion's downloadable app.

BIOTRILLION LIFEDATA APP

The purpose of LIFEdata s to generate broad-based LIFEdata from our users. For users to be willing to use the app consistently requires high levels of engagement from our users. We believe engagement can be summarized by the following equation: Engagement = Value / Friction. (Ancillary to this is Value = Outcomes / Costs.) In other words, user engagement is maximized when the user receives a high amount of value and encounters the least amount of friction while using the App as possible.

ASSUMPTIONS

This product plan contains substantial foundational decisions governing the eventual output. Below are Assumptions as we know them that influence these decisions. June 2019.

Device	iPhone Series X	iPhone Series XR	iPhone Series XS	iPhone Series XS Max
	Body ▫ *150.9 x 75.7 x 8.3 mm (5.94 x 2.98 x 0.33 in)* ▫ *194 g (6.84 oz)* Display ▫ *OLED capacitive touchscreen, 16M colors* ▫ *5.8 inches, 84.4 cm2 (~82.9% screen-to-body ratio)* ▫ *1125 x 2436 pixels, 19.5:9 ratio (~458 ppi density)* ▫ *Scratch-resistant glass, oleophobic coating* ▫ *Dolby Vision* ▫ *HDR10* ▫ *Wide color gamut* ▫ *3D Touch* ▫ *True-tone* ▫ *120 Hz touch-sensing* Platform ▫ *Apple A11 Bionic (10 nm)* ▫ *Hexa-core 2.39 GHz (2x Monsoon + 4x Mistral)* ▫ *Apple GPU (three-core graphics)* Platform ▫ *64/256 GB, 3 GB RAM* ▫ Rear-facing Camera ▫ *12 MP, f/1.8, 28mm (wide), 1/3", 1.22µm, PDAF, OIS* ▫ *12 MP, f/2.4, 52mm (telephoto), 1/3.4", 1.0µm, PDAF, OIS, 2x optical zoom* ▫ *Quad-LED dual-tone flash, HDR (photo/panorama), panorama, HDR* ▫ *2160p@24/30/60fps, 1080p@30/60/120/240fps* Front-facing Camera ▫ *7 MP, f/2.2, 32mm (standard)* ▫ *TOF 3D camera* ▫ *HDR* ▫ *1080p@30fps* Sensors ▫ *Accelerometer* ▫ *Barometer* ▫ *Dot projector* ▫ *Flood illuminator*	Display ◦ *IPD LCD capacitive touchscreen, 16M colors* ◦ *6.1 inches, 90.3 cm2 (~79.0% screen-to-body ratio)* ◦ *828 x 1792 pixels, 19.5:9 ratio (~458 ppi density)* Platform ◦ *Apple A12 Bionic (7 nm)* ◦ *Hexa-core (2x2.5 GHz Vortex + 4x1.6 GHz Tempest)* ◦ *Apple GPU (4-core graphics)* ◦ *64/256/512 GB, 4 GB RAM* Rear-facing Camera ◦ *12 MP, f/1.8, 26mm (wide), 1/2.55", 1.4µm, PDAF, OIS* ◦ *2160p@24/30/60 fps, 1080p@30/60/120/240fps, HDR, stereo sound rec.* Sensors ▫ *Ambient light sensor* ▫ *Dot projector* ▫ *Flow illuminator* ▫ *Infrared camera (depth sensing capability only)* ▫ *Three-axis gyro*	Body ◦ *143.6 x 70.9 x 7.7 mm (5.65 x 2.79 x 0.30 in)* ◦ *177 g (6.24 oz)* Display ◦ *OLED capacitive touchscreen, 16M colors* ◦ *5.8 inches, 84.4 cm2 (~82.9% screen-to-body ratio)* ◦ *1125 x 2436 pixels, 19.5:9 ratio (~458 ppi density)*	Body ◦ *157.5 x 77.4 x 7.7 mm (6.20 x 3.05 x 0.30 in)* ◦ *208 g (7.34 oz)* Display ◦ *6.5 inches, 102.9 cm2 (~84.4% screen-to-body ratio)* ◦ *1242 x 2688 pixels, 19.5:9 ratio (~458 ppi density)* ◦

		▫ *Infrared camera (depth sensing capability only)* ▫ *Microphone* ▫ *Proximity sensor* ▫ *Speaker* ▫ *Gyro*			
OS	iOS 12+ key capabilities	ARKit Document Scanning (Notes app) HealthKit Indoor Maps / Lane Guidance Live Photo Editing Options			
Tech Architecture	BioEngine4D	TBD –2019/2020			
	Data Stores	User Population Biomarkers Disease Detection and Prediction			
	3rd Party Integration	TBD (Ops?)			
	Target User, Use Case	Average consumer, Potential investors Predictable, consistent environment; ideal ambient lighting (bedtime)			
	Light Source-Stimuli-Related	Rear-facing Flash: Its intensity is determined by BioTrillion to be enough to trigger a PLR response. However, it can't produce different wavelengths, which is deemed to be a valuable stimuli variation. The front-facing OLED display brightness and sufficiency to trigger a sufficient PLR response Ambient Light; incidental lighting Face/feature Reflection			
Target User	Goals	Consumer Professional Scientific, Medical			
	Use cases	consumer performance use Professional performance use Scientific or Clinical-grade use			
	Skills	Background Science Medicine Technology e.g., (hardware, software, communication network)			
	Frequency of Use	One time Several times Repeat- independent of time interval			
Business	Investment	Frequency Dollar amount Level of control			
	Profit	High/low importance			
	Growth	High/low importance			
Limitations	Hardware	Capabilities of iPhone X ◦ *Access to full IR capability* ◦ *Device-local computation* ◦ *Peak performance without WIFI* No hardware aids ◦ *Attachable devices (lenses, mirrors lighting, etc.)* ◦ *Props (mirrors, lamps, tri-pods, selfie sticks, etc.)*			
	Software	• Factory installed (default) software			

		◦ *HealthKit* ◦ *ARKit*
	User Experience	Front-facing camera experience Independent of second or third or more parties ◦ *Not require help from other people in order to operate at peak performance* ◦ *More than one user use-cases are valid (e.g. build community experience) but not primary*
	Environmental: Points in time / space	Time-of-day independent Functional Indoors and outdoors ◦ *However, peak for some capabilities (e.g. optical capture) may be possible indoors* Amenable to variable capture conditions ◦ *Same or nearly the same to achieve performance requirements* Amenable to Inconsistent capture session conditions ◦ *Peak performance despite changes in time, place (e.g., bedroom at night vs daytime at beach)*

SUCCESS METRICS

IMPLEMENTATION PRIORITY LEVELS

These guidelines govern the order of importance and priority of implementation associated with goals, tasks, features, etc.

P0	Highest Priority	Required Absolutely must to be implemented
P1	High Priority	Not required Critical product success component Critical to achieving stated business objectives Implemented once P0 features are/will be assuredly implemented (per accountability rules)
P2	Medium Priority	Not required Critical product success component Not critical to achieving stated business objectives Nice to have but may not be implemented
P3	Low Priority	Not required Not critical product success component Not critical to achieving stated business objectives May be implemented in future release
P4	Unimportant	Will not be implemented

PRODUCT PERFORMANCE

These guidelines provide a framework for monitoring product performance and health. Provides foundation for analytics.

Q0	Optimal	Highest possible quality Accurate Timely Sustained Consistent
Q1	Excellent	High quality Exceeding requirements
Q2	Adequate	Good quality Meeting requirements
Q3	Failing	Poor quality Not meeting requirements At risk of failure
Q4	Broken	Not functional

IMPLEMENTATION PLAN

Implementation phases are divided into workstreams to de-risk development and reduce potential bottlenecks.

BioTrillion's disease detection platform is being developed over four phases:

PHASE 0: Disease expression pathway modeling optimal LIFEdata variables selection — Ongoing

Identity optimal LIFEdata phenotypic features, non-molecular expressions of diseases, based on clinically validated pathophysiology that can become digital biomarkers once relationships between them and diseases (or via well-validated molecular biomarkers) are drawn.

PHASE 1: LIFEdata Generation and Data Aggregation — In progress, as outlined in this SOW

Leverage the iPhone's optical modality (the first of multiple planned sensor modalities) sensors to digitally biomark key eye and facial features to Neurology and Dermatology disease targets that yield the greatest (1) statistical accuracy and (2) return on early intervention.

The PHASE 1, WORKSTREAM 1 will focus on novel features of greatest importance and most technically challenging to implement; each requires substantial research and experimentation. there are few, if any, known precedents to learn from and build on.

The time and resources needed to execute on PHASE 1 are the least predictable. Accordingly, development requires greater than average schedule padding and cross-team communication management to be resilient to potential delays and increase the likelihood of meeting delivery schedules and ultimate product launch. This SOW pertains to one or more PHASE 1 workstreams and is a sub-set of the overall Product Requirements Document (PRD).

WORKSTREAM 1: PLR TECHNOLOGY DEVELOPMENT

P0 - Generating data through pupillary response measures (such as the PLR)
P1 - Capture of sclera and iris features, in additional to facial skin and topology

WORKSTREAM 2: FULL OPTICAL MODALITY DEVELOPMENT

P0 - Sclera and iris features
P1 - Facial skin and topology

WORKSTREAM 3: IPHONE APP EXPERIENCE

P0 - Phenotype capture, data generation and processing

- *Optical measures*

P0 - First-time and repeat user experiences
P1 - Authentication, User accounts and profiles
P1 - HealthKit integration
P1 – Analytics, tracking (technology, user experience performance)

WORKSTREAM 4: BACK-END ARCHITECTURE AND OPERATION

P0 - Software and hardware architecture
P0 - Data storage and retrieval
P0 - Data privacy and security

PHASE 2: Analytics: Data processed by BioEngine4D into Digital Biomarkers — 2019/2020

By applying machine learning and neural networks, LIFEdata can become digital biomarkers when relationships are drawn between them and diseases, or via well-validated molecular biomarkers. Disease detection and prediction incorporates analysis multidimensional and scalar LIFEdata and Medical data.

PHASE 3: Applications digitally detecting developing disease Biomarkers — 2020

Neuro and Derm disease detection. Version 2.0 iPhone app. Securely connecting smart device sensors to generate novel LIFEdata measures and yield quantified, dynamic, and more granular health insights.

PHASE 1: LIFEDATA GENERATION AND AGGREGATION

OPTICAL MODALITY WORKSTREAM

Goal

Produce an Alpha-quality prototype capable of generating reliable and repeatable optical LIFEdata data from the eye. Achieving this goal assumes a well-defined set of performance metrics, which are discussed above.

Pupillary Response Measures, Including Pupillary Light Reflex (PLR)

PLR is the highest priority feature of this prototype. Given the expected time and cost to develop, it provides the most immediate value to customers and to development of BioEngine4D compared to other measures in BioTrillion's roadmap.

BioTrillion seeks to offer repeatability, accuracy, and precision of a pupillometer with the ubiquity and convenience of a penlight by using a technology that most people have within arm's reach: a smartphone.

To achieve this there are three things that we need to solve given the limitations of today's most sophisticated smartphones:

Intensity of the stimulus light.

Intensity gradient between stimulus light and ambient illumination.

Wavelengths of stimulus light.

VALIDATION AND TESTING

There are five quantitative PLR assessment measures that will be determined through testing and validation of the this prototype.

- ***Latency (ms)**: time between the beginning of the light stimulus and the start of pupil constriction*
- ***Constriction velocity (mm/s):** speed at which pupil constricts; reported as mean or max.*
- ***Constriction amplitude (mm):** difference between the max pupil diameter before and after light stimulation.*
- ***Constriction percentage (%):** the constriction amplitude expressed as a percentage of the initial size.*
- ***Dilation velocity (mm/s):** the speed at which the pupil dilates; reported as mean or max.*

Measure	Clinical Standard		BioTrillion Target	
	Penlight	Pupillometer	Rear-facing camera and flash	Front-facing camera and display
Latency (ms): Ground truth range Mean absolute error *Standard deviation of absolute error*	TBD	TBD	TBD	TBD
Constriction velocity (mm/s): Ground truth range Mean absolute error Standard deviation of absolute error			 0.37-8.99 1.78 0.67	TBD
Constriction amplitude (mm): Ground truth range			 0.32-6.02	TBD

Mean absolute error Standard deviation of absolute error			0.62 0.72	
Constriction percentage (%): Ground truth range Mean absolute error Standard deviation of absolute error			 6.21-62.00 6.43 6.74	TBD
Dilation velocity (mm/s): Ground truth range Mean absolute error Standard deviation of absolute error			 0.37-8.99 1.78 0.67	TBD
Steady-state baseline pupil size				

DATA QUALITY

Measurement quality is determined by three criteria: according to specific levels of accuracy, reproducibility.

- *Accuracy - conformity of an indicated value to an accepted standard.*
- *Reproducibility – closeness to repeated measurements under varying operating conditions over long time periods.*

*Accuracy & Reproducability Targets**

Highest accuracy and lowest error.

I. Reproducibility of Results.

II. Consistency from from iPhone, to pupillometer type A, to pupillometer type B, from user 1 to user 2 to user 3; lighting conditions X to lighting conditions Y to lighting conditions Z.

III. Measurements (pupil diameter) at 0.04 and 0.4 lux ambient illumination.

Incentive Structure

Accuracy per Metric for Ground Truth Data and Test Session-specific Data

Service Criteria	Target Measures								Threshold	Service Incentive
	Mean	Minimum	Maximum	SD	SD/Mean (%)	Pearson's R Between Eyes	Mean Difference	SD of the Difference		
Ratio P/I in darkness	0.59	0.50	0.67	0.04	6.8	0.90	-0.001	0.023	< 0.04	+ 0.05
Latency time for constriction	0.17	0.11	0.27	0.03	17.6	0.39	0.028	0.063	< 0.03	+ 0.05
Amplitude P/I of largest % deviation	0.45	0.35	0.56	0.05	11.1	0.92	0.005	0.019	< 0.05	+ 0.05
Amplitude P/B of largest % deviation	0.76	0.66	0.90	0.06	7.9	0.96	0.010	0.033	< 0.06	+ 0.05
Latency of largest % deviation	0.64	0.50	0.83	0.07	10.9	0.95	0.015	0.098	< 0.07	+ 0.05

Amplitude P/I of plateau	0.55	0.47	0.62	0.04	7.3	0.90	0.006	0.017	< 0.04	+ 0.05
Amplitude P/B of plateau	0.93	0.84	0.99	0.04	4.3	—	—	—	< 0.04	+ 0.05
Latency of plateau	2.04	1.44	2.44	0.23	11.3	0.13	0.075	0.302	< 0.23	+ 0.05
Duration of constriction	1.86	1.27	2.27	0.24	12.9	0.09	-0.100	0.303	< 0.24	+ 0.05
Total work (P/I)	0.19	0..07	0.31	0.06	31.6	0.82	-0.014	0.048	< 0.06	+ 0.05
Total work (P/B)	0.63	0.52	0.75	0.07	11.1	—	—	—	< 0.07	+ 0.05
Number of oscillations	4.10	3.00	6.00	0.99	24.1	0.13	0.577	1.027	< 0.99	+ 0.05

Mean values, minimum, maximum, standard deviations and reliability (Pearson product moment correlation coefficient for difference between L and R eyes) of variables for the (single flash stimulation).(1)

P/1, variables based on the ratio pupil : iris

P/B, variables based on the ratio pupil : baseline

** Differences between two measurements*

Accuracy per Milestone Completion Date

Milestone	Target Completion	Incentive	
		Under	Over
Front-facing Camera Placement	07.15.19	+ 0.05	
Stability of Photo/Video Capture	07.22.19	+ 0.05	
Optimum screen lux	07.15.19	+ 0.05	
Optimum flash duration	07.15.19	+ 0.05	
Binocular capture	07.29.19	+ 0.05	
One-eye capture	07.29.19	+ 0.05	
Pupil Diameter accuracy	07.29.19	+ 0.05	
Accuracy gauge on per use basis	07.29.19	+ 0.05	

		June	July	August	September	October	November	December
Engineering: Pupillary Light Reflex	Front-facing Camera Placement							
	Stability of Photo/Video Capture							
	Optimum screen lux							
	Optimum flash duration							
	Binocular capture							
	One-eye capture							
	Pupil Diameter accuracy							
	Accuracy gauge on per use basis							
Eng: Infrastructure, Security	Architecture							
	Implementation							
Eng: App								
User Experience	Field Studies							
	Architecture, Nav Model							
	Screen Design							
	Visual Design							
Privacy								
Business								

PROJECT SCOPE

The objectives of the proposed project, to be discussed with BioTrillion, are as follows:

1. Refine understanding of problem understand nature of qPLR to measure, relevant stimuli characteristics and measurement practices in medical settings.
2. Refine our review of the iPhone XS's tech specs¨ available actuators and sensors.
3. Perform initial tests on whether the front-facing display is capable of triggering qPLR responses.
    a. In this viability instance the scope of the tests would be limited to determine whether PLR is observable in specific conditions, rather than finely determining the capabilities and limitations of the OLED display as a stimulus source.
4. Review relevant state of the artª implement and evaluate an initial viability Prototype on iPhone XS validation videos.
    a. For the purpose of obtaining quick viability results with no algorithmic constraints in this first instance, the prototype will be implemented for desktops/laptops and using Python libraries.

PROPOSED TASKS

- Refine problem analysis.
    - Verify whether there is indeed no useful IR data accessible on the iPhone XS for this task.
- Review relevant state of the art articles.
- Define initial capture protocol for iPhone XS videos that will be used for validation.
- Record videos following protocol.
- Manually annotate pupil segmentation ground truth on selected videos to create an initial viability validation dataset.
- Implement pupil segmentation viability prototype on iPhone XS evaluation videos.
- Write project reports.

DELIVERABLES

- Viability prototype source code.
- Annotated viability validation dataset.
- Technical report including:
    - Refined problem analysis.
    - Review of relevant state of the art articles.
    - Detail of viability prototype algorithms.
    - Quantitative performance results on the viability prototype.
    - Main conclusions and recommendations for next steps.

PROJECT TEAM AND METHODOLOGY

The team will be composed by one of our senior consultants and one or two R&D Engineers (all of them with extensive knowledge and experience in Image Processing), although the entire team of senior consultants will be available for consultation on their areas of expertise. We suggest to have weekly e-meetings of no more than half an hour to do the follow up of the project, but additional e-meetings will be certainly needed to discuss/analyze options and approaches.

	Pupillary Light Reflex	Iris Deposits	Sclera Color	Skin Color	Skin Topology
Reproducibility					
Baseline (FDA)	Less than 5% test-retest variability in pupil diameter measurements.	Repeatability of less than 3 RGB for a minimum of one measurement.	Less than 10% test-retest variability in CIE XYZ value.	Repeatability of 2x greater than next leading measurement tool.	Less than 5% test-retest variability in skin depths and optical resolution.
BioTrillion	TBD	TBD	TBD	TBD	TBD

Accuracy					
Baseline (FDA)	Pupil diameter measurements within 90%	HSL (Hue, Saturation, Luminance) measurements within 85-90%	CIE measurements within 90-95%	ITA (Individual Topology Angle) within 90%	Images of skin depths within 90-95%
BioTrillion	TBD	TBD	TBD	TBD	TBD

BioTrillion's research suggests that reaching the deliverable goal is likely dependent on the results of several process steps. We bring them to your attention as potentially helpful clues. This is list is not comprehensive and BioTrillion is not suggesting that these steps be followed. We rely on your expertise and processes to reach the deliverable goal.

1. *Design reproduceable test protocol for obtaining relevant and reliable pupillary response data to support training of Machine Learning algorithms.*

- *Confirm viability of the five qPLR measures as producing relevant data.*
- *Identify and validate precedent studies to build on*
  - *Perform initial testing on whether the front-facing display is capable of triggering qPLR responses. The scope of the tests would be limited to determine whether PLR is observable in specific conditions, rather than finely determining the capabilities and limitations of the OLED display as a stimulus source.*

- *Obtain and classify a large data set of images, with sample diversity across a number of different dimensions to ensure adequate, broad coverage, suitable for expert training.*
- *Define the numbers of categories into which each pupil endpoint will be scored, and the standards for expert labeling, identify labeling resource.*
- *Determine minimum standards for numbers and capture parameters for images in each of the desired categories.*
- *Determine how to best capture and prepare testing data for next processing step as well as method for storing and sharing data.*

2. *Investigate other ways to resolve light intensity issues via Determine which generations of iPhone X must be included when building ground truth data.*

3. *Compare performance of prototype with industry-recognized and trusted device in user in present day.*

DELIVERABLES

At the conclusion of the engagement, BioTrillion requires the following:

- *Functional prototype that performs a PLR Measurement via front-facing camera at an accuracy of 90%.*
- *Validation of Accuracy and Repeatability as the best way to measure quality; recommend useful, potentially superior alternative performance measures with success/failure threshold scale*
  - *Metrics are not limited to PLR functionality; propose metrics for tracking overall system health (technology architecture, security, etc.)*

- *Platform architecture proposal comprising but not limited to the BioTrillion Phone app, BioEngine4D and supporting components.*
- *Method for generating, analyzing and reporting LIFEdata – for processing by BioEngine4D.*
- *Device-local data processing independent of WIFI.*
- *Final source code, specifications and other supporting documentation. Prioritized outline of existing and proposed features and functionality*
-

ACCEPTANCE CRITERIA

Establishes measures to determining level of completion

- *Computer science (e.g. Computer Vision, AI), medical consultants together with BioTrillion will draft appropriate criteria to assess level of completion and quality.*

WORKSTREAM 2: BIOTRILLION MOBILE APPLICATION EXPERIENCE

Goal

Develop a consumer experience that envelopes the Optical Modality, introducing users to BioTrillion's value proposition and delivering it. This takes the form of a traditional smart phone app though additional 'components' may be necessary to deliver a compelling experience. The resulting app will launch to the Apple App Store.

Development includes:

- *Market and user research*
- *Experience design Branding and marketing*
- *Front-end engineering*
- *Back-end engineering.*
-

Design

Step 2 will require market and user research use case development and validation (via rapid prototyping for example), integration of user experience with optical modality functionality (where technical complexity gives way to intuitive, usable interface): navigation model, visual and functional design (i.e. screen and hardware interaction design).

Branding

The MVP will need to define and represent the BioTrillion's identity and message, app identity, and look and feel (i.e. typography, symbology, composition, color, written language and tone).

Engineering

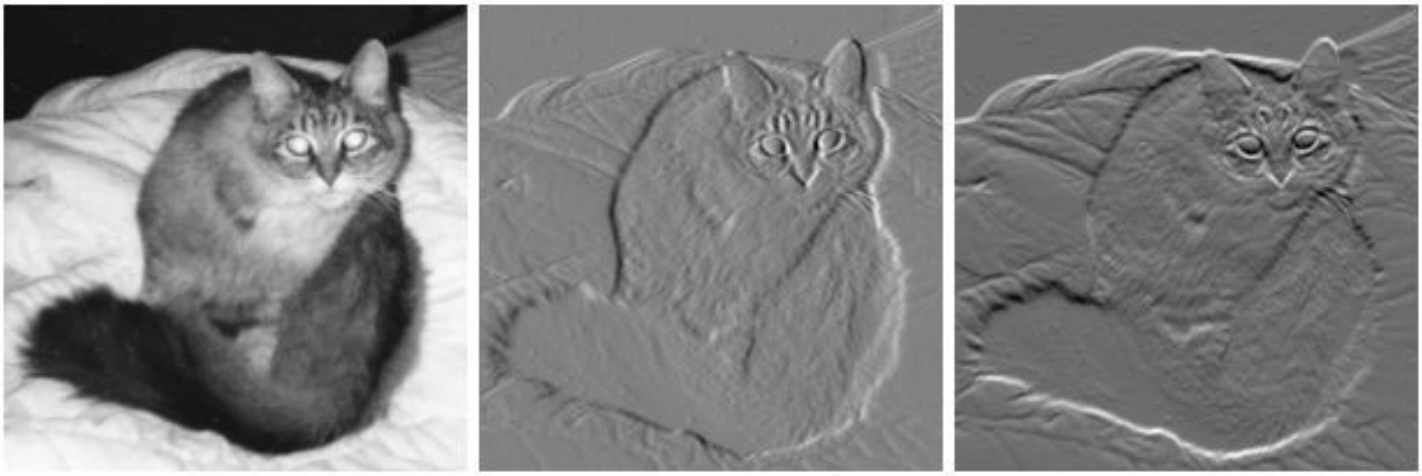
- *Define build out of backend architecture, including integration with third-party technologies; front-end coded representation of app experience, branding and integration with backend engineering; and a web administration dashboard, along with various integrations, including but not limited to e-mail and SMS.*

Engineering approach expectations for each feature above, with a focus on the PLR given the published research behind it and its clinical research backing.

ADDENDUM

KEY FEATURE ENGINEERING

One of the main risks that we believe should be addressed at this point, is the ability to segment the pupil on a highly pigmented iris. In the visible portion of the electromagnetic spectrum (visible light), the iris could be very dark, making it very difficult to see its internal boundaries (that is, where the iris ends and where the pupils begin).



During the last conversation between BioTrillion and dSense, it was clarified that it is not strictly necessary to segment the pupil frame by frame, since what is really important is to determine how the pupil changes between them. BioTrillion already performed a number of tests analyzing these changes. It was noticed that the boundaries of the pupil are clearly visible by analyzing the relative changes between frames.

It is a well-known fact that changes between frames can give a lot of information about the scene. Techniques such as Optical Flow are based on this principle. Indeed, the visual system is much more adapted to local changes than to global ones. Most of image processing techniques (including all the ones based on ML approaches with Convolutional Neural Networks) base their image interpretation on the local changes of an image. When considering derivatives in the (x,y) coordinates, what is obtained is a measure of the local changes within a scene:

PUPILLARY RESPONSE MEASURES

The clinical gold standard for measuring the PLR uses a device called a pupillometer. Pupillometers are expensive (~$4500 USD) and are mainly used in hospitals. Another is through a penlight exam, where a clinician directs a penlight towards the patient's eyes and observes the pupils' responses. This is simple to perform, but has drawbacks, including a lack of standardization, a need for deliberate training, and poor inter-observer reliability. Penlight exams are used in emergency first aid situations rapid assessment is prioritized over precision. BioTrillion seeks to offer repeatability, accuracy, and precision of a pupillometer with the ubiquity and convenience of a penlight by using a technology that most people have within arm's reach: a smartphone.

This can be easily extended to a sequence of images adding time as an additional dimension (based on the extracted millisecond time delta between frames captured in a video of at least 120 frames/second; The information obtainable in this case are the changes between frames —basically, the movement within the scene.

PUPIL SEGMENTATION AND EXTRACTION

Pupil segmentation ("Segmentation") and extraction of key spatial and temporal ("Feature Extraction Metrics1") from a frame-by-frame time-series video sequence of a Pupillary Light Reflex generated by the front-facing optical hardware of an iPhone X or above ("PLR Video").

Pupil diameter as a function of time

The mechanics of the pupil, the pathophysiology of the PLR, and the diagnostic power of the PLR.

A normal PLR is defined as symmetric constriction or dilation of both pupils in response to a light stimulus or its absence, respectively. The pupil size must change by a non-trivial amount within a specified time frame and should change in both eyes, regardless of which eye is stimulated. For example, when a person covers one eye while the other is exposed to bright light, the pupils of both the covered and exposed eyes should constrict, producing a phenomenon known as the consensual response. The pupil size must change by a non-trivial amount within a specified time frame and should change in both eyes, regardless of which eye is stimulated. For example, when a person covers one eye while the other is exposed to bright light, the pupils of both the covered and exposed eyes should constrict, producing a phenomenon known as the consensual response.

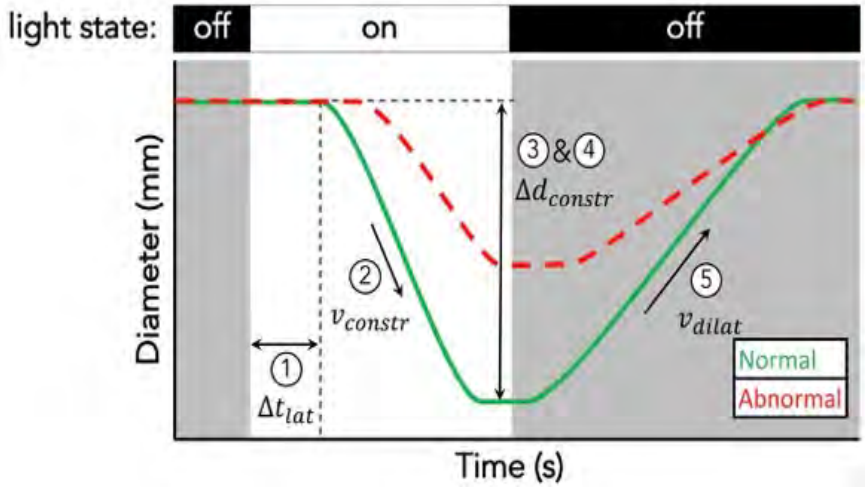


Figure 1 A PLR curve annotated with five common descriptive measures:

(1) latency,
(2) constriction velocity,
(3) constriction amplitude,
(4) constriction percentage, and
(5) dilation velocity.

An abnormal PLR curve with increased latency, slower velocities, and diminished amplitude is also included for comparison.

Latency – Time taken for each pupil to respond to a light stimulus measured in milliseconds (ms).
Maximum Diameter – The maximum diameter observed measured in millimeters (mm).
Maximum Constriction Velocity – The maximum velocity observed over the constriction period (mm/ms).
Average Constriction Velocity – The average velocity observed over the total constriction period (mm/ms).
Minimum Diameter – The minimum diameter observed (mm).
Dilation Velocity – The average velocity observed over the total dilation period (mm/ms).
75% Recovery Time – The time take for each pupil to reach 75% of its initial diameter value (ms).
Average Diameter – Average of all diameter measurements taken in a time series measured in mm.

PROPOSED METHODOLOGY FOR CAPTURING IRIS DEPOSITS

	Feature	Pupillary Response Measures, Including Pupillary Light Reflex (PLR)
1	Facial Coordinates	Automatic detection of pixel-based eye and tip-of-nose locations (3 reference points) – ensures trigonometric and spatial consistency of measurements. Moderately-facilitated alignment by user, with machine-algorithmic assistance. E.g. an on-screen circle matches location and size of pupil and iris.
2	Pupil Presence	Machine vision algorithm detects facial coordinates, even if face moves across camera field of vision. Input loaded as gray-scale video. If face is detected, system proceeds to detect pupil. If pupil not present, users notified that video doesn't meet criteria for effective qPLR.
3	Light Stimulus	When phone nears optimal spatial distance from face, app notification signals imminent screen light stimulus. Size of pupil constriction increases as contrast between front-facing iPhone OLED screen flash and threshold ambient light level (dark room) increases.
4	Data Capture	HD Pupil video recording (30-60+ frames/sec) automatically carried out on app. Set of still images produced. Perhaps a baseline image prior to capture will be created.
5	Image Processing	Crop filter image to obtain region of interest (ROI): brightness, RBG and saturation thresholds set. Demarcate pupil-iris boundary: filtered ROI images converted to gray scale to improve contrast. Shape analysis: scan remaining pixels for contour, convex shapes; filter at pre-set circularity thresholds. Following capture, unnecessary information will be eliminated by establishing cropping bounds, excluding information such as the pixels around the eye socket, and the pixels above the eyelid towards the eyebrow. One illustrative potential methodology for image processing, as outlined by another app, is as follows: Crop image to region of interest (ROI) Filter pixels based on brightness, color values, to determine pixel filtering thresholds in these steps: ◦ *May use HSV values – hue, saturation, brightness value. E.g. the device may filter out pixels having a "V" value (which represents brightness) of greater than 60.* ◦ *Or LAB values – "L" = Brightness of pixel, "A" and "B" for color-opponent values. Because pupils are the darkest feature of the eye, app may filter out pixels having an L-value greater than 50, thereby leaving only the pixels which are relatively darker and more likely to include the pupil.* Duplicate the resulting image, discarding what has been filtered out to just show ROI Convert filtered ROI pixels to grey scale. Filter grey scale pixels based on brightness or intensity values ◦ *E.g. device may filter pixels having an L (brightness) value higher than 45* Scan remaining pixels for contours and convex shapes ◦ *Scans for incremental gradients in grey scale pixel values, constructs contour-based/defined shapes.* Filter those shapes based on size and circularity ◦ *E.g. a circle may have a circularity value at or near 1.0, while an elongated ellipse may have a circularity value of around 0.25. Thus, the device filters out values which are not at or around 1.0* Determine surface area of pupil and iris regions, so relative change in these two regions can be measured.
6	Key PLR Feature Qualification	Imaging analysis software algorithms determine pupil size measured across recorded images. Relative change in surface area of pupil region vs. iris region correlates to the change in pupil radius. Detection metrics: constriction latency, velocity, amplitude, percentage (and relevant dilation metrics). Variation in measures relative to a retrospectively established longitudinal baseline (individual) can be indicative of a disease state or a performance measure for disease.

"LOWER BOUNDARY OF AMBIENT LIGHT NEEDED FOR PUPIL SEGMENTATION USING IPHONE X"

This number will need to be experimentally determined either internally or by our software developers following the completion of an image capture/segmentation prototype. There is no official cutoff lux value below which the segmentation is officially not possible. That being said:

- *Experiments conducted by the University of Washington for the development of PupilScreen found that brown eyes led to the worst results, and their process uses a box that eliminates ambient light altogether. Mean pupil diameter errors were +0.27mm for brown eyes, compared to +0.24mm and +0.07mm for blue and mixed eyes, respectively, in conditions with 0 ambient light. The most extreme outliers in the study also belonged to participants with particularly dark irises. (https://atm15.github.io/pdfs/pupilscreen.pdf)*

- *On the other hand, a study conducted for the development of AlertnessScanner had 9 brown-eyed participants in the first part of their study (out of 20) and 4 in the second (out of 8), and reported mean ambient lighting conditions for image capture ranging from 16.2 - 336.5 lux and 62.7 - 177.4 lux for the two phases of the study, respectively. They reported no specific difficulty in segmenting the pupils to compute pupil-to-iris ratio from their brown-eyed participants. (http://pac.cs.cornell.edu/pubs/AlertnessScanner.pdf)*

- *A study investigating the correlation between PLR and iris color was able to segment the pupil from brown iris to extract significant metrics under background illumination of 0 lux. (https://www.ncbi.nlm.nih.gov/pubmed/9717650)*

- *A study on mobile eye tracking actually found that brown eyes were easier to track: "Blue eyed subjects do not have as clear a contrast between the iris and the pupil as brown eyed subjects, making the device presumably more accurate on brown eyed individuals", but didn't find this error substantial as many subjects with blue eyes used the eye tracking device with no more noticeable difficulty than the brown eyed subjects. This study, however, does not indicate their lighting conditions. (https://pdfs.semanticscholar.org/aa10/3045c4eec106c664037e86ad48fd671b819b.pdf)*
-
- *A study on iris pattern distortion with varied ambient lighting conditions looked at pupil size variation under different normal indoor lighting conditions (100 lux ~ 1200 lux). Participants included Asian individuals with dark brown irises. The study reported no difficulty in segmenting pupils from dark irises. The range of average pupil sizes under normal lighting conditions for a controlled environment was between 3mm and 4mm for illumination levels between 200 to 1000 lux. The range of average pupil ties was found to be between 6.46 - 6.55mm for 50 lux illuminance. (https://eprints.qut.edu.au/16672/1/Shiau_Shing_Phang_Thesis.pdf)*

IMAGING ANALYSIS SOFTWARE ALGORITHMS

The imaging analysis software algorithms will determine pupil size parameters across a series of recorded images. Since the elapsed time is known between each image (frames per second), the rate at which the pupil size changes over time can be determined. Frames in the sequence must be smoothed to de-noise the system of natural fluctuations in the pupil, color variance in the irises, as well as variance caused by the device itself. A Gaussian smoothing operator will be used to slightly blur the images and reduce noise.

$$G_\sigma(x,y) = \frac{1}{2\pi\sigma^2}\exp^{-\frac{x^2+y^2}{2\sigma^2}}$$

This 2D Gaussian equation:sigma is the standard deviation of distribution. PLR are represented as Fourier transformations; smoothing the Fourier transform yield an easily understood graph. Using a histogram representation of smoothed grayscale frames, a threshold function binarizes the images.

This threshold function can be determined by the distinction between dark and light pixels on the histogram. Based on this, the images can be binarized in such a way that distinguishes the sclera from the pupil by labelling white parts of the image with a 1, and black parts of the image with a 0. This effectively generates a black square with a white circle representing the pupil clearly for analysis. Pupils are generally shaped as ellipses but can be represented as a circle by averaging the axes. Diameter can be measured in pixels between the two white pixels farthest away from each other. This pixel measurement can be converted to millimeters using a fiducial of known dimensions held near the eye.

This 2D would yield a more easily understood graph. Using a histogram representation of the smoothed grayscale frames, a threshold function will binarize the images.

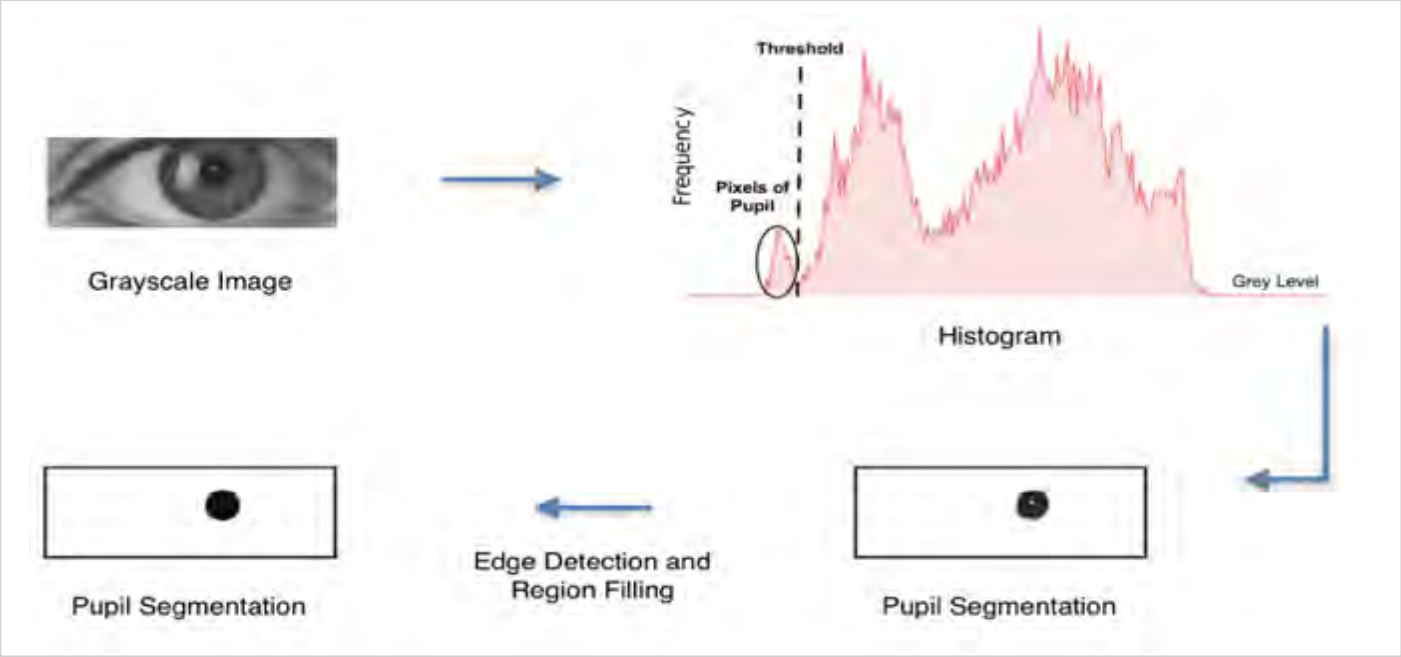
.

$$M(D) = \tanh^{-1}\left(\frac{D - 4.9}{3}\right)$$

$$\frac{\mathrm{d}M}{\mathrm{d}D}\frac{\mathrm{d}D}{\mathrm{d}t} + 2.3026\tanh^{-1}\left(\frac{D - 4.9}{3}\right) = 5.2 - 0.45\ln\left(\frac{\Phi[t - \tau]}{4.8118 \times 10^{-10}}\right)$$

The differential equation that describes a pupillary light reflex in terms of pupil diameter flux as a function of light is as follows:

Quantitative pupil segmentation workflow



PLR is typically broken into several components:

• Constriction latency is measured as tflash - tinitial constriction, i.e., the time between flash onset and start of pupil constriction.

• Constriction velocity is a measure of the rate at which the pupil constricts in millimeters/second.

• Constriction amplitude is measured as (Dmax prior to light exposure) - (Dmin following light exposure), where D is the pupil diameter.

• Constriction percentage is measured by taking constriction amplitude as a percentage of Dmax; dilation velocity is a measure of the rate at which the pupil dilates in millimeters/second.

• These metrics comparable to PLR curves of healthy individuals in order to identify abnormalities.

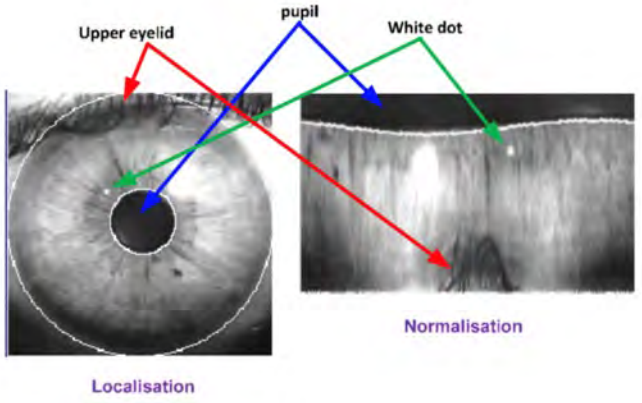
PROPOSED METHODOLOGY FOR CAPTURING IRIS DEPOSITS

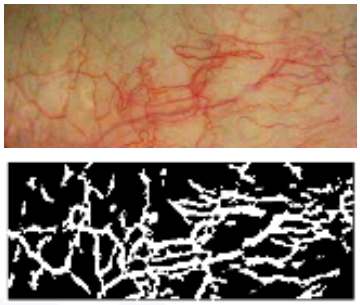
	Feature	Iris Deposits
1	Iris recognition	Automatic detection of pixel-based eye and tip-of-nose locations (3 reference points)– ensures trigonometric and spatial consistency of measurements. ◦ *Moderately-facilitated alignment by user, with machine-algorithmic assistance.*
2	Segmentation	Demarcate region of interest (ROI): inner iris pixels from outer-boundary iris (limbus). Determine threshold iris circle parameters (radius + center coordinates). Determine threshold circle parameters circle (radius + center coordinates) for pupil iris regions (e.g. using Hough Transform). ◦ *This segmentation (localization) process is to search for the center coordinates of the pupil, iris and their radius. These coordinates are marked ci,cp where ci is represented as the parameters [xc, yc, r] of the limbic and iris boundary, cp is represented as the parameters [xc, yc, r] of the pupil boundary. It uses [6] to select the possible center coordinates first. The method consists of threshold followed by checking if the selected points (by threshold) correspond to a local minimum in their immediate neighborhood these points serve as the possible center coordinates for the iris.* ◦ *These radius values were set manually; the input for this function is the image to be segmented and the input parameters in this function including rmin and rmax (the minimum and maximum values of the iris radius). The range of radius values to search for was set manually, depending on the database used.* ◦ *This function's output is the value of ci and cp which is the value of [xc, yc, r] for the pupillary and limbic/iris boundaries and the segmented image. As discussed above, this process uses The Hough.*
3	Normalization	Convert circular iris shape to rectangular shape to give radius value for pupil and iris. Incidence of Arcus Senilis (iris cholesterol deposit): a yellow-white ring around the cornea occurring from the limbus up to 30% through iris towards the pupil. Crop normalized image to 30% full image. ◦ *From the normalization process, the segmented image of the eye gives the value radius of the pupil and iris. This image is cropped based on iris radius value, so the unwanted area is removed (e.g. sclera and limbic), Arcus Senilis is described as a yellowish-white ring around the cornea that is separated from the limbus by a clear zone 0.3 to 1 mm in width.* ◦ *Normally the area of white ring (Arcus Senilis), occurs from the sclera/iris up to 20-30% toward to pupil, thus this is the only the important area that must be analyzed. In rectangular shape analyze can be done either from top to bottom or from bottom to top. (J. Daugman, 2004) describes details on algorithms used in iris recognition. He has introduced the Rubber Sheet Model that transforms the eye from circular shape to rectangular form. It is shown in Fig.1.* ◦ *This model remaps all point within the iris region to a pair of polar coordinates (r,□□where □the angle is [0,2□□and r is on the interval [0,1] .Since the pupil can be non-matching with the iris therefore it needs to remap to rescale the points depending to the angle around the pupil and iris.*

4	Calculation	Identify optimum threshold to detect Arcus Senilis. Quantitative assessment of Arcus Senilis. Variation in measures relative to a retrospectively established longitudinal baseline (individual) can be indicative of a disease state or a performance measure for disease. ◦ *Cholesterol detection starts by obtaining number of normal eyes and illness eye images (Arcus Senilis). The next step is to isolate the actual iris region in digital eye image. The isolation process needs to be done to segment the outer boundary for the iris and the inner boundary for the pupil. This can only be done by searching the center point of the pupil given by x and y axis. Hough transform is used to detect edge of the iris and pupil circle.* ◦ *The algorithm processes the image with the MATLAB software; the image from the database gives wrong detection on pupil boundary because segmentation on pupil is on the illumination light rather than segmenting the pupil boundary. This will fail to determine the edge of the pupil, but it will detect the edge of the impurity illumination light, which will affect the segmentation quality eye image, cause imperfection in detecting the iris and pupil boundary region of the eyes. But luckily the significant area of white ring (Arcus Senilis) lay at the boundary of sclera or iris up to the pupil, so long as the segmentation done correctly on the iris it can considered succeed.* ◦ ◦ *This segmentation image will be crop is based on the value of iris's radius. Even though the pupil boundary is not accurately detected in this segmentation process, these images still can be accepted since the incidence of cholesterol normally occur from limbic up to pupil which is 30 percent from overall normalization image. Therefore, for this kind of segmentation it is better to consider the correct segmentation of iris boundary rather than pupil boundary segmentation.* ◦ *Next, the image must be analyzed, and this can only be done if it is transformed to normalized polar coordinates using Rubber Model. Since the "sodium ring", terminology given in iridology, or Arcus Senilis for the grayish or whitish arc in iris is only available at the bottom of this coordinate, thus only 30% of the iris part is considered in the normalization.* ◦ *Lastly, to determine whether the eye has the ring, and image histogram must be plotted. The algorithm assumes the image contains two classes of pixels (e.g. foreground and background) and finds the optimum threshold separating the two classes so that their combined spread (within-class variance) is minimal.*

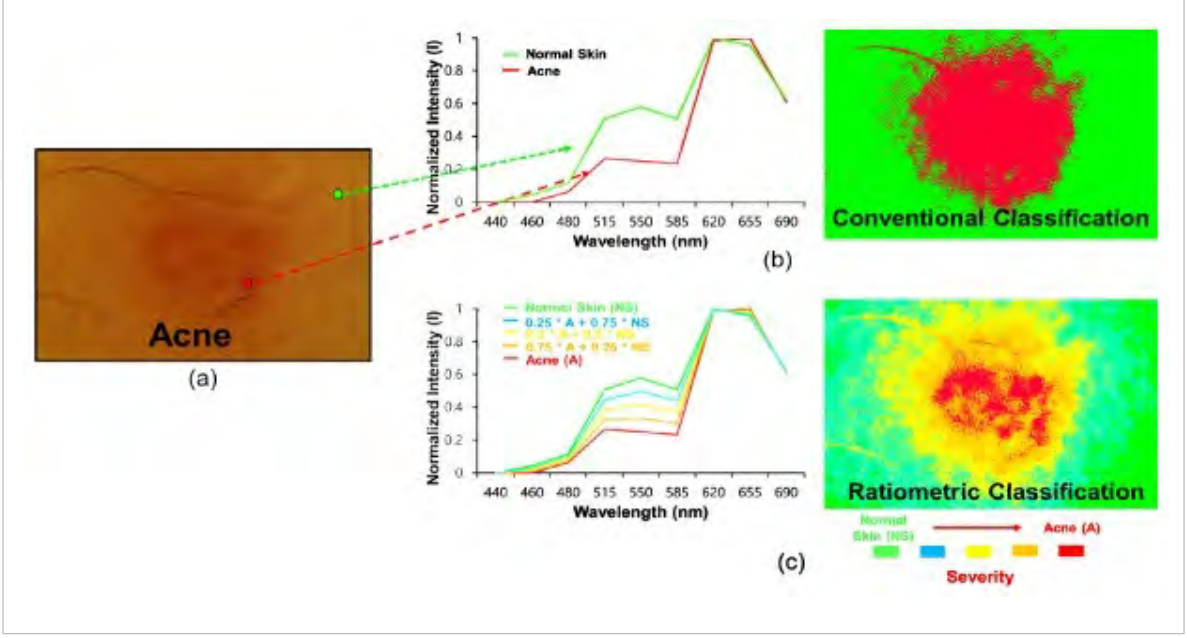
SCLERA VASCULATURE

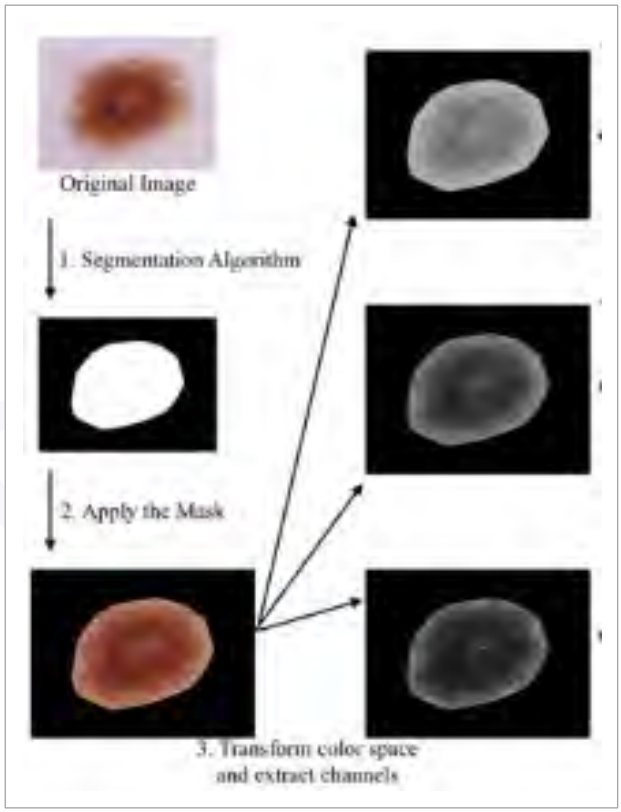
The following methodology is proposed for capturing sclera vasculature features:

	Feature	Sclera Vasculature	
1	Iris recognition	Automatic detection of pixel-based eye and tip-of-nose locations (3 reference points)– ensures trigonometric and spatial consistency of measurements. Moderately-facilitated alignment by user, with machine-algorithmic assistance.	
2	Segmentation	Demarcate rectangular sclera area from iris.	

		Sclera, skin, and reference color (white patch) pixel coordinates are identified in an image viewer. Classify pixels into foreground (blood vessel) and background (white sclera). Normalization of iris from circle to rectangle. Color balancing: RGB color indexes are produced for sclera, skin and reference color. Produce a binary image (black background, white veins).
3	Normalization	Convert circular iris shape to rectangular shape to give radius value for pupil and iris. Incidence of Arcus Senilis (iris cholesterol deposit): a yellow-white ring around the cornea occurring from the limbus up to 30% through iris towards the pupil. Crop normalized image to 30% full image. From the process of normalization, the segmented image of the eye gives the value radius pupil and the iris. This image will be cropped base on the value of iris radius, so that the unwanted area will be removed (e.g. sclera and limbic), Arcus Senilis is described as a yellowish-white ring around the cornea that is separated from the limbus by a clear zone 0.3 to 1 mm in width.  Normalization of iris from circle to rectangle [2] Normally the area of white ring (Arcus Senilis), occurs from the sclera/iris up to 20 to 30 percent toward to pupil, thus this is the only the important area that must be analyzed. In rectangular shape analyze can be done either from top to bottom or from bottom to top. (J. Daugman, 2004) describes details on algorithms used in iris recognition. He has introduced the Rubber Sheet Model that transforms the eye from circular shape into rectangular form and it is shown in Fig.1. This model remaps all point within the iris region to a pair of polar coordinates (r,□□□where □the angle is [0,2□□□ and r is on the interval [0,1] .Since the pupil can be non-matching with the iris therefore it need to remap to rescale the points depending to the angle around the pupil and iris. Critical for sclera feature analysis is color identification and analysis using sclera and skin pixel coordinates (for comparison). Reference color, manually identified in an image viewer, is represented by a white patch in the color chart. Three indexes —Red (R), Green (G) and Blue (B)— are calculated by averaging 900 neighboring pixels (30 × 30 region) centered on pre-defined pixel coordinates. These color indexes result: Reye, Geye and Beye for sclera, Rskin, Gskin and Bskin for skin, and Rref, Gref and Bref for reference color. Normalized color indexes are also calculated for sclera and skin (e.g., Reye,nor = Reye / Rref is the normalized sclera red color index. In digital photography, normalization is considered a color balancing process.
4	Calculation	Quantitative assessment of scleral vasculature. Variation in measures relative to a retrospectively established longitudinal baseline (individual) can be indicative of a disease state or a performance measure for disease.

The following methodology is proposed for capturing skin surface/topology (3D) features:

	Feature	Skin Color
1	Recognition	Automatic detection of pixel-based eye and tip-of-nose locations (3 reference points)– ensures trigonometric and spatial consistency of measurements. Moderately-facilitated alignment by user, with machine-algorithmic assistance.
2	Segmentation	Determine facial regions of interest (ROIs).
3	Normalization	Assign each skin pixel an R, G and B intensity value. Convert filtered image to gray-scale. Shading correction and spectral calibration reduces discrepancies created by non-uniform illumination. Additional research needs to be done around skin color feature engineering, but once a color image capture of the skin is done, each skin pixel is assigned a R, G, and B intensity values. Those are then converted to gray-scale using the following equation: 1/3 * (R + G + B). Then shading correction and spectral calibration are done via calculations to reduce discrepancies created by non-uniform illumination using the equation below: $$I_{cal}(x,y,\lambda) = I_{origin}(x,y,\lambda) \times \frac{WT_{max}(\lambda)}{WT(x,y,\lambda)} \times w_c(\lambda)$$ Where Ical (x, y, λ) denotes the calibrated intensity at x, y, and λ, Iorigin (x, y, λ) is the original intensity of the pixel at x, y, and λ, wc (λ) is the weight factor for calibration at the wavelength of λ, WTmax (λ) is the maximum intensity on the white target at λ. WT (x, y, λ) is the intensity of the white target at x, y, and λ. *Spectral Imaging to assess acne lesions.* 

4	Calculation	Quantitative assessment of skin coloration. Variation in measures relative to a retrospectively established longitudinal baseline (individual) can be indicative of a disease state or a performance measure for disease.
		Automatic detection of pixel-based eye and tip-of-nose locations (3 reference points)– ensures trigonometric and spatial consistency of measurements. Moderately-facilitated alignment by user, with machine-algorithmic assistance.
		D Example of skin topology segmentation algorithm. [1] Example of skin topology segmentation algorithm. [1]  *Example of skin topology segmentation algorithm.* [1]
		Assign each skin pixel an R, G and B intensity value. Convert filtered image to gray-scale. Shading correction and spectral calibration to reduce discrepancies created by non-uniform illumination. Additional research needs to be done around skin topology feature engineering, but once a color image capture of the skin area with a lesion is done, each pixel is assigned an RGB value between 0 and 255. Then, each pixel is converted to grayscale and a segmentation threshold is calculated for each image. Finally, the segmented image is converted to a binary image, in which all the lesion's pixels are assigned a value of 255 (white) and healthy skin pixels are assigned 0 (black).
		Quantitative assessment of skin coloration. Variation in measures relative to a retrospectively established longitudinal baseline (individual) can be indicative of a disease state or a performance measure for disease.

ANTICIPATED R&D CHALLENGES

Give the unprecedented nature of this project, BioTrillion expects to face multiple R&D before launching a successful App: Energy stimulus: The project will require a front-facing iPhone screen flash to catalyze pupil response to replace current rear-facing smartphone LED flash.

True Depth and IR: The project may require leveraging the IR and True Depth cameras in the smartphone for enhanced optho-anatomic segmentation.

Local Processed Feature Extraction: Features extracted from the eye/face need to be computationally processed on-device, ensuring privacy and future HIPAA compliance. Only de- identified numbers go to BioEngine4D cloud for further analytics.

Quantifying the Previously Qualified: Although PLR has been measured quantitatively, the other features do not have clear precedent of quantitative measurement. R&D will be required to determine how best to quantify them.

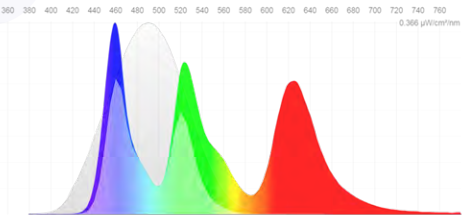
R&D Challenge #1: Energy Stimulus

A truly unprecedented and novel innovation in qPLR will require 2 key breakthroughs:

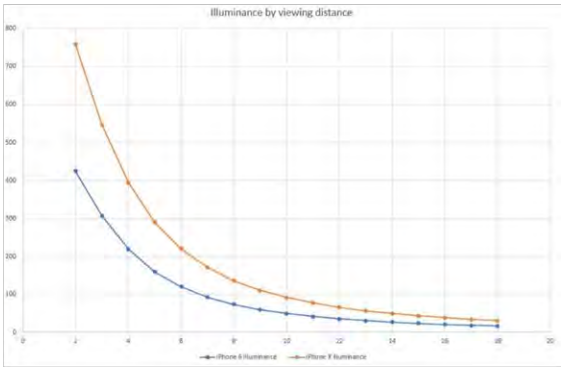
#1: Generating photonic energy from front screen to catalyze full reflex

In order to verify qPLR's feasibility, BioTrillion must develop a front-facing iPhone screen flash (consumer tool) to replace current rear-facing smartphone LED flash (clinical tool)

1. **BioTrillion's Research.**
   - iPhone X OLED screen peak brightness – luminance (or "nits") = **726 cd/m²** [1]
   - iPhone X OLED screen (at 9in viewing distance [2]) – melanopic lux = **>110 cd/m²** [3]
   - iPhone X rear flash – luminous flux = ~**50 lumens** [4]
   - **Our calculations show** iPhone X OLED screen **maximum brightness as ~75% an iPhone flash.**
   - We expect that an iPhone X screen is sufficient to initiate a full neurological pathway cascade (parasympathetic and sympathetic) and generate a sufficient qPLR response.
2. **Determine threshold ambient light level.**
   - A contrast between dark and bright light must be achieved to maximize pupil constriction. We predict that a dark-room (pre-sleep) is a good setting for qPLR.
3. **Localize PLR to light only.**
   - Three pupil reflexes exist: pupil light response (PLR), pupil near response (PNR) & psychosensory pupil response (PPR). PLR is only part reflexive, it is modulated by many high-level cognition factors: visual awareness, covert visual attention, eye-movement preparation, and subjective brightness. [5]



Spectral sensitivity graph for iPhone X OLED screen: melanopic region (gray). Melanopsin is a retinal pigment sensitive to "blue-green" light [3]



iPhone 6 vs. X luminance-distance graph [3]

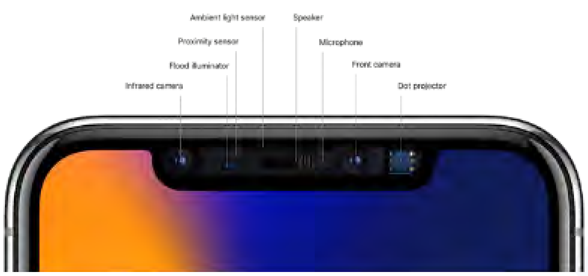
1. http://www.displaymate.com/iPhoneXS_ShootOut_1s.htm#Brightness_Contrast
2. https://www.ncbi.nlm.nih.gov/pubmed/21499163
3. https://justgetflux.com/news/2018/02/16/OLED.html
4. https://www.quora.com/How-bright-is-the-LED-flashlight-on-the-iPhone
5. https://www.journalofcognition.org/articles/10.5334/joc.18/

R&D Challenge #2: True Depth and IR

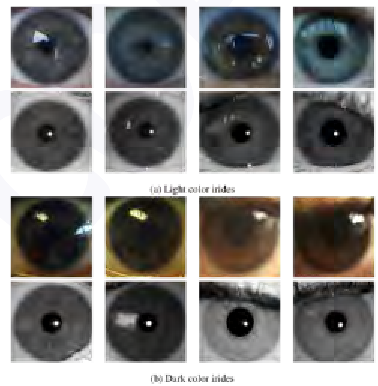
#2: IR access on front-screen for enhanced optho-anatomic segmentation

qPLR is difficult to achieve in ambient lighting conditions but infrared (IR) light (700 to 1000 nm) helps distinguish characteristics between pupil and iris.

- IR provides high-resolution information for analysis but loses meta information relating to colorimetric data in iris region. Converting filtered images to gray-scale improves pupil-iris contrast. [1]
- Apple's FaceID is a biometric scanner built into the front-facing TrueDepth iPhone X camera. It projects >30,000 IR dots to form a series of IR depth maps of the face. [2]
- Apple's AR Kit for Developers allows access to the TrueDepth camera. Raw access to IR camera is unavailable, but cloud and point depth data can be streamed from IR and dot sensors. [3]



Apple iPhone X TrueDepth Camera. [1]



First row of each a and b: iris in visible light. Second row of each a and b: iris in IR light. Segmentation at iris-pupil boundary of dark irises is easier with IR light. [1]

1. https://static1.squarespace.com/static/[illegible]/Evaluation+of+Reflex+and+its+Applications+in+Medicine_KS_RR_JS_V2.pdf
2. https://www.apple.com/business/site/docs/FaceID_Security_Guide.pdf
3. https://developer.apple.com/documentation/arkit/creating_face-based_ar_experiences

R&D Challenge #3: Locally Processed Feature Extractions

#3: Features extracted from the Eye/ Face need to be computationally processed on-device, ensuring Privacy and future HIPPA Compliance. Only de-identifiable #'s go to BioEngine4D cloud for further analytics.

Local feature extraction processing is the ideal to meet consumer privacy requirements.

- App makers must obtain "clear and conspicuous consent" from users before collecting and storing facial data, providing data is not sold to 3rd parties and can only be used for a legitimate app feature.[1]
- "Model protection": non-remote, non-cloud/server-based. On-app processing allows you to train AI model on device, with both user data and BioTrillion's model protected.[2]

1. https://www.businessinsider.com/apple-face-id-developers-save-face-data-2017-11
2. https://www.fritz.ai/features/model-protection.html

DATA ARCHITECTURE AND PROCESSING OF DATA

Engineering will determine the appropriate model(s) and architecture for capture, analysis, generation, storage, sharing, querying, and other processing of the data above. Critically, as discussed above, BioTrillion's goal is to ensure that feature extraction and analysis will be done locally, i.e., on the user's device and not in the cloud.

- *Priority number one is to run the app exclusively from the device so that users who are not connected to the internet can still use the app.*
- *If a cloud component must be established, and the app cannot fully run on the device:*
- *Define a core set of features that can run locally without need for internet connection*
- *Define the set of power features that require a stable internet connection*
- *For use cases dependent on an internet connection, conceal heavy processing and data exchange so users do not perceive noticeable performance lag*
- *Establish measurable and trackable performance goals. Run performance and budgeting experiments, micro-optimization, and track outcomes.*
- *Ensure approach taken will be amenable to HIPAA-compliant privacy and security.*

Engineering will also have to define performance metrics and budget and assign a performance value to each feature to quantify impact on user experience.

DEVELOPMENT STEPS

1	User Interface Design (UI)	Creating the visual language of the LIFEdata App using composition, typography, colors, element styling. Includes content creation and curation (basic placeholder copywriting, imagery, illustrations, icon sets), and consistency and standards (assuring the interface adheres to modern mobile standards of similar platforms and the given operating system).
2	Wireframes - Low-Fidelity (UX)	Wireframe blueprints of the LIFEdata App (as defined during kickoff) to help display functionality, flow, and how information will be displayed. Some color, icons, and photos included to make the experience more realistic for the user.
3	Clickable Prototype Development (UI)	Stitching individual screens together into a clickable prototype utilizing the InVision tool.
4	Information Architecture (UX)	Mapping out of application structure by developing a framework for organizing product information in modules related to a stakeholder task. This will be compiled into a document displaying hierarchy and organization of the App content representing the way a user will navigate.
7	Rapid Software Prototyping	Rapid creation of software prototypes of the novel features to confirm assumptions, viability and determine optimal approaches according to a mutually agreed level of fidelity and polish such that BT invests not in design but in the technical features/functionality.
8	Software Testing & Validation	Testing and validation of software prototypes for measurements of each of the five LIFEdata features of pupillary light reflex, iris deposit features, sclera color features, skin color features, and skin topology features. Measurements of these features will be tested and validated against specific levels of accuracy, reproducibility, and possibly repeatability. "Accuracy" is defined as the conformity of an indicated value to an accepted standard. Reproducibility is defined as the closeness of agreement among repeated measurements under the varying operating conditions over longer periods of time. Repeatability is defined as the closeness of agreement among repeated measurements under the same operating conditions over shorter periods of time. See image in Step 1 for an overview of testing and validation criteria, along with gold standards of measurement.
9	Technical Direction	Overall technical management of the duration of the project.
10	Product Management	Oversees overall product development cycle from ideation to launch in the store. Will serve as main point of contact for design and development management. Additional responsibilities include setting up business logic, user stories, QA, assistance with beta and full App deployments.
11	Design Review & Project Alignment	Client review for feedback and preliminary approval before completion of the whole App UX/UI design is conducted. Design needs, approach, proposal, costs, and timeline will be presented and agreed upon following completion of core technical features.

FRONT-END APP

1	Login	As a returning user, I will need the ability open/access the App by providing a username/password, Google, or Facebook
2	New User Onboarding	As a new user, I will be introduced to the platform. I will need the ability to register a new account by providing an email/password. I will review and accept the platform Terms and Conditions. I will be introduced to LIFEpoints. I will set up my account and personally enter my existing medical data
3	Home Screen	As a user, I will need an intuitive way to navigate between different user flows within the App and view my current HEALTHscore.

4	Physiologic Systems Screen	As a user, I will be able to view and explore my HEALTHscore measures for my physiological systems.
5	Data Tab and Data Visualization Screen	As a user, I will be able to view and explore my HEALTHscore data in a variety of useful and informative ways.
6	Health Tips Screen	As a user, I will learn how to improve my HEALTHscore and be encouraged to act. Note: this functionality relies upon content being supplied by client.
7	About Me Screen	As a user, I will be able to view and manage my account information including my data sources, settings, medical data, saved content, notifications and messages, and personalized offers.
8	Informational Content	As a user, I will be able to access up-to-date content regarding the factors that affect my health. Note: this functionality relies upon content being supplied by client. This is low priority in comparison to core BT app features such as PLR and can be done independently of technical work, contingent on successful completion of PLR goals.
9	Integrations	The LIFEdata mobile application will feature integrations with a host 3rd party API's (e.g. HealthKit, Google Fit). It will be determined during Kickoff and On-boarding sessions what limits (if any) will be in in the first phase of development and then gradually expanded to other platforms in later phases of the product roadmap.
10	Passive Data Gathering	The LIFEdata mobile application will gather and store a host of passively generated data regarding the state of the user's health. Note: this functionality will rely upon the integration with HealthKit and rely upon the user to be actively utilizing another wearable device or tracking system to pull in this data via 3-party API's (e.g. HealthKit, Google Fit).
11	Active Data Gathering	The LIFEdata mobile application will gather and store a host of actively generated data regarding the state of the user's health via a variety of methods including surveys and by actively utilizing device sensors such as the forward-facing camera. Note: Survey functionality relies upon content being supplied by client. It is recommended that survey functionality be moved to a later phase of the product roadmap.
12	Settings	As a user, I will need the ability to edit/control preferences (push notifications, etc.).
13	Error Handling	Alerts, notifications, and communication to user when errors affecting usage occur (ex: feature unavailable due to data signal loss, or unexpected LIFEdata App v1 downtime).
14	Static Pages	Privacy Policy, Terms of Use, FAQs
15	Push Notifications	As a user, I will need to receive push notifications to alert me when there is an automatic or custom message for me
16	Analytics & Event Tracking	App analytics to track user's behavior throughout the app.
17	IxD Implementation	Implement the IxD animations from design
18	Language Support	Enabling users to communicate in non-English languages. This is low priority in comparison to core BT app features such as PLR and can be done independently of technical work, contingent on successful completion of PLR goals.
19	QA	Quality Assurance testing
20	Code adjustments after QA	Adjustments to code once Quality Assurance has taken place
21	LIFEdata App v1 Store Submission	Deploy application on to iTunes store for download (Includes screen shots)
22	Technical Direction	Technical Management
23	Project Management	Project Management

BACK-END DESCRIPTION

1	User Roles	Create user roles and associated DB structure.
2	Authentication / Authorization	Authenticate and authorize users. This is low priority in comparison to core BT app features such as PLR and can be done independently of technical work, contingent on successful

		completion of PLR goals.
3	HEALTHscore Module	Aggregate data and rate HEALTHscores for various physiological systems.
4	Active Data Collection & Processing Module	Collect and analyze survey data and sensor measured physiological data (such as images of the face and eye structures)
5	Image Processing/Machine Learning Module	Integrations and processes for processing of images generated by the user to generate usable data regarding physiological health indicators. Tasks such as developing deep neural network architectures for the purpose of extracting clinically-relevant knowledge from imagery (sound, movement, etc.) as well as timing must each be specifically defined, scoped, prioritized and scheduled For example, Absent pre-existing ground truth PLR data, this is expected to take significant time.
6	QA	Quality Assurance testing + bug fixes
7	Code Adjustments after QA	Adjustments to code once Quality Assurance has taken place
8	Technical Direction	Technical Management
9	Project Management	Project Management

WEB APPLICATION (ADMIN DASHBOARD)

1	Secure private login	User authentication for secure login
2	Admin Controls	Create, Read, Update, Delete, Search API data
3	Platform Usage Analytics	View analytics on the way in which users are utilizing the app
4	User Rights Management	Control user rights and accounts
5	Notifications & Messaging	Send notifications and messages to users of the platform
6	Quality Assurance	QA testing + debugging
7	Technical Direction	Web Technical Management (Admin Dash)
8	Project Management	Project Management

APP UI/UX DEVELOPMENT

Once engineering is successful, the mobile app developer will be required to move to Step 2, the development of the front-end mobile application. BioTrillion has done a significant amount of product-market fit research to inform the user experience, and that research will be provided to the development partner. We also will provide examples of other mobile applications that have created a compelling UI/UX for users. The app developer will also have to design a user interface and incorporate third-party integrations, initially only with Apple HealthKit.

PHILOSOPHY

The purpose of LIFEdata App v1 is to generate broad-based LIFEdata from our users. For users to be willing to use the app consistently requires high levels of engagement from our users. We believe engagement can be summarized by the following equation: Engagement = Value / Friction. (Ancillary to this is Value = Outcomes / Costs.) In other words, user engagement is maximized when the user receives a high amount of value and encounters the least amount of friction while using the App as possible.

INTEGRATIONS AND MEDICAL DATA

For the first release of our application, we want to integration only with Apple HealthKit. In later versions of our app, we will integrate with other APIs, such as FDA MyStudies and Veterans Health API, as well as with directly with other apps.

Apple HealthKit will serve as a source of Medical Data as well as passively collected data, such as steps, heart rate, and ECG.

PROJECT SCOPE

1. *Design reproduceable test protocol for obtaining relevant and reliable pupillary response data to support training of Machine Learning algorithms.*

- *Confirm viability of the five qPLR measures as producing relevant data.*
- *Identify and validate precedent studies to build on*

- *Perform initial testing on whether the front-facing display is capable of triggering qPLR responses. The scope of the tests would be limited to determine whether PLR is observable in specific conditions, rather than finely determining the capabilities and limitations of the OLED display as a stimulus source.*

- *Obtain and classify a large data set of images, with sample diversity across a number of different dimensions to ensure adequate, broad coverage, suitable for expert training.*
- *Define the numbers of categories into which each pupil endpoint will be scored, and the standards for expert labeling, identify labeling resource.*
- *Determine minimum standards for numbers and capture parameters for images in each of the desired categories.*
- *Determine how to best capture and prepare testing data for next processing step as well as method for storing and sharing data.*

2. *Investigate other ways to resolve light intensity issues via Determine which generations of iPhone X must be included when building ground truth data.*

3. *Compare performance of prototype with industry-recognized and trusted device in user in present day.*

ALPHA PRODUCT

PUPILLARY LIGHT REFLEXT (PLR)

The pupillary light reflex is when miosis (pupil constriction) occurs as a reaction to light. This reflex——————————————————is the body's natural response to bright lights and its purpose is to prevent excessive stimulation of the optic nerve that could lead to temporary visual deficits. Neurological issues can be inferred from its result (i.e. a sluggish response may indicate that the patient is undergoing cerebral edema or herniation). Measurement and tracking of the pupil size over time can also inform clinicians about neurological status (e.g. pinpoint pupils may be indicative of an opiate overdose or a pontine hemorrhage stroke).

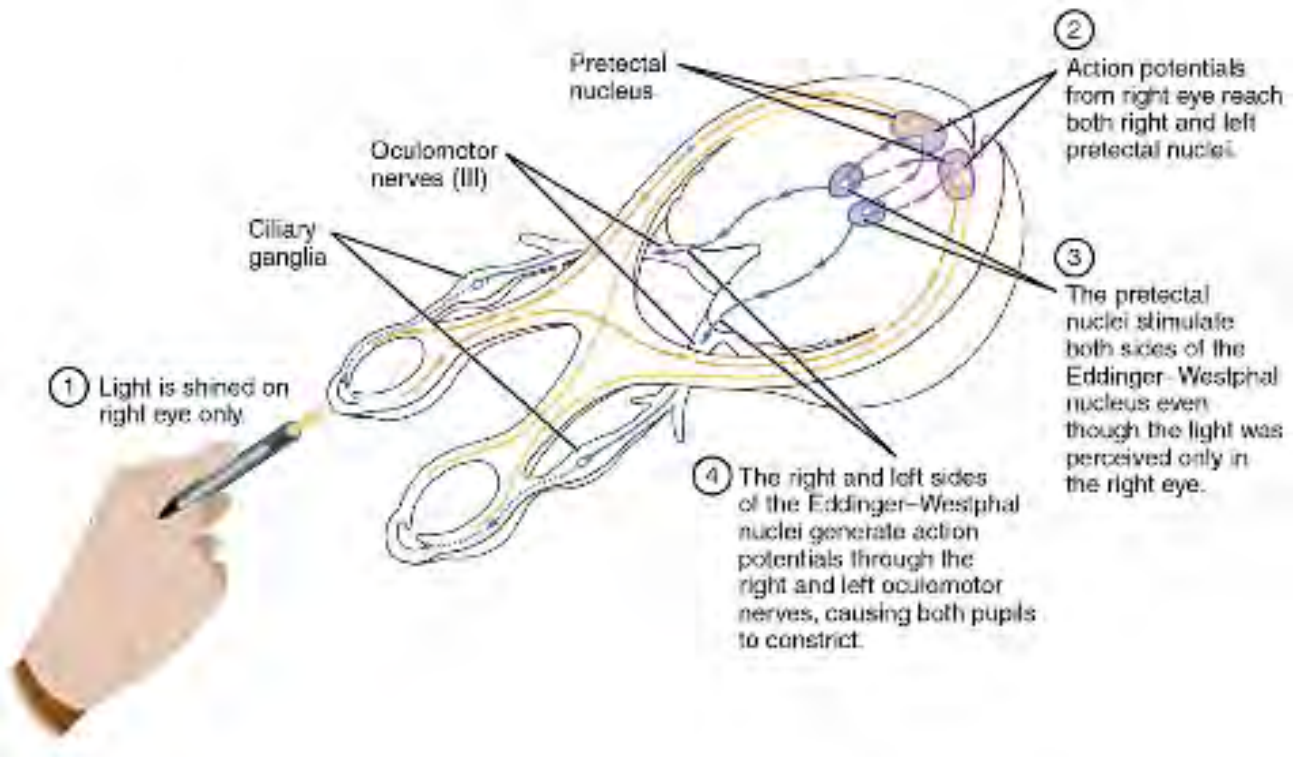


Figure 1: *Pathway of Pupillary Light Constriction*

PLR IN NEUROLOGICAL ASSESSMENT

Basic methods of assessing the pupillary light reflex use a flashlight and involves the clinician's subjective assessment, while advanced methods involve expensive and specialized medical equipment. With an accessible and accurate app to track changes in the aforementioned neurological assessment components detected by BT, clinicians can save lives by initiating earlier treatment. BioTrillion (BT) also has broader potential in healthcare applications for the research of depression, Alzheimer's, sleep, diabetes, multiple sclerosis and other diseases [].

BEHAVIOR	DESCRIPTION	CONDITION
	Unilateral dilated pupil	III nerve compression (90% ipsilateral to haematoma)
	Bilateral dilated pupils	Midbrain injury
	Irregular pupils	Orbital trauma
	Equal and reactive	When one pupil is exposed to light, both pupils identically constrict.
	Small / pinpoint	Pontine injury, opiate administration
	Conjugate gaze deviation	Frontal lobe lesion

Figure 2: *Pupillary Abnormalities*

Figure 3: *The GCS score is used as an objective measurement of responsiveness that enables clinicians to quantify a patient's level of consciousness.*

In a hospital setting, neurological assessments are performed routinely depending on the acuity of the patient (e.g. every 1 to 4 hours per patient). Neurological assessments consist of the Glasgow Coma Scale (GSC) and pupillary light reflex test, which enables clinicians to infer whether any neurological issues require further medical attention.

The PLR component of BioTrillion's app was designed to replicate the neurological assessments that are regularly conducted by clinicians in the hospital. BT fits into a clinician's workflow almost seamlessly; in the same way a clinician would pick up and fill a patient's chart following a GCS assessment, the clinician selects the patient, enters the 'Test Centre' and inputs GCS results followed by performing the pupillary light reflex test.

The Neuroptic NPI Pupillometer, a pupillometer device used in hospitals, influenced the visual layout of the pupillary light reflex implementation. The block diagram, below, displays the high-level relationship of BT's various components and will be discussed in itemized detail below.

Glasgow Coma Scale

BEHAVIOR	RESPONSE	SCORE
Eye opening response	Spontaneously	4
	To speech	3
	To pain	2
	No response	1
Best verbal response	Oriented to time, place, and person	5
	Confused	4
	Inappropriate words	3
	Incomprehensible sounds	2
	No response	1
Best motor response	Obeys commands	6
	Moves to localized pain	5
	Flexion withdrawal from pain	4
	Abnormal flexion (decorticate)	3
	Abnormal extension (decerebrate)	2
	No response	1
Total score	Best response	15
	Comatose client	8 or less
	Totally unresponsive	3

Figure 3: *The GCS score is used as an objective measurement of responsiveness that enables clinicians to quantify a patient's level of consciousness.*

FUNCTIONAL COMPONENTS

App Home is the primary screen that allows users to navigate to the various functional areas of the application ('Test Centre', 'Patient History' and 'Patient Manager'). It populates a dropdown menu from the patient database to facilitate quick patient selection.

Test Centre allows the user to navigate between the neurological assessment components (GCS and pupillary light reflex). When the user leaves the Test Centre, it saves all results to the database.

Glasgow Coma Scale (GSC) facilitates entry of the GCS scores.

Pupillary Light Reflex facilitates the pupillary light reflex using the device camera and flash. It does this by recording a video of the eye, during which, the phone's flash will turn on for 1 second to stimulate the reflex. Then the video is processed, and the results of the processing are displayed back to the user.

OpenCV Processing is the primary processing block of our app. It takes the recorded video frame-by-frame and determines the size of the pupil in each, the framerate of the video is then used to calculate the speed of constriction.

Interpreter is an algorithm that assigns a qualitative value of “Brisk”, “Sluggish”, or “Absent” to describe the constriction speed of the pupil.

Patient History is a user interface component that displays the selected patient’s past test in a timestamped table with a plot of the data shown above. The results for GCS, pupil size, and pupillary reflex speed are on separate pages.
size, and pupillary reflex speed are on separate pages.

Patient Database is where all the data is stored and where it is retrieved from.

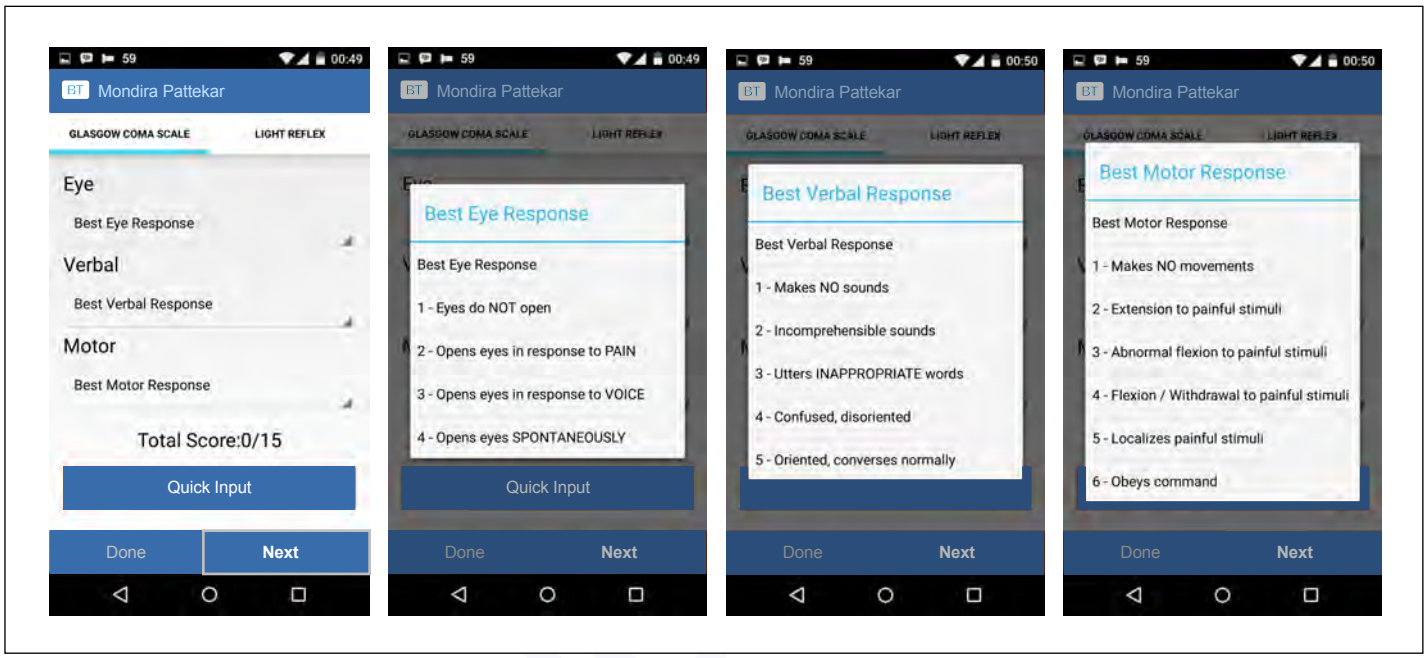


Figure 3: *The Glasgow Coma Scale test interface (left) and input dialogues (right).*

GLASGOW COMA SCALE (GCS) TEST

The GCS test page provides a way for the user to score the patient’s responses following an assessment. The user can individually select each popup spinner, or press the “Quick Input” button (Figure 4). “Quick Input” automatically opens the next input window, reducing the number of selections the user has to make from 6 to 4, improving the user experience.

PUPILLARY LIGHT REFLEX TEST

The pupillary light reflex test measures the size (diameter) and constriction speed of the patient’s pupil, and classifies this constriction speed into one of three categories: brisk, sluggish, or absent.

The user is prompted to fit a red circle over the patient’s iris. The red circle defines the region that will establish a reference scale that is used to translate the pupil’s size to an absolute measurement in millimeters (assuming the iris size is 12 mm; average human iris size.

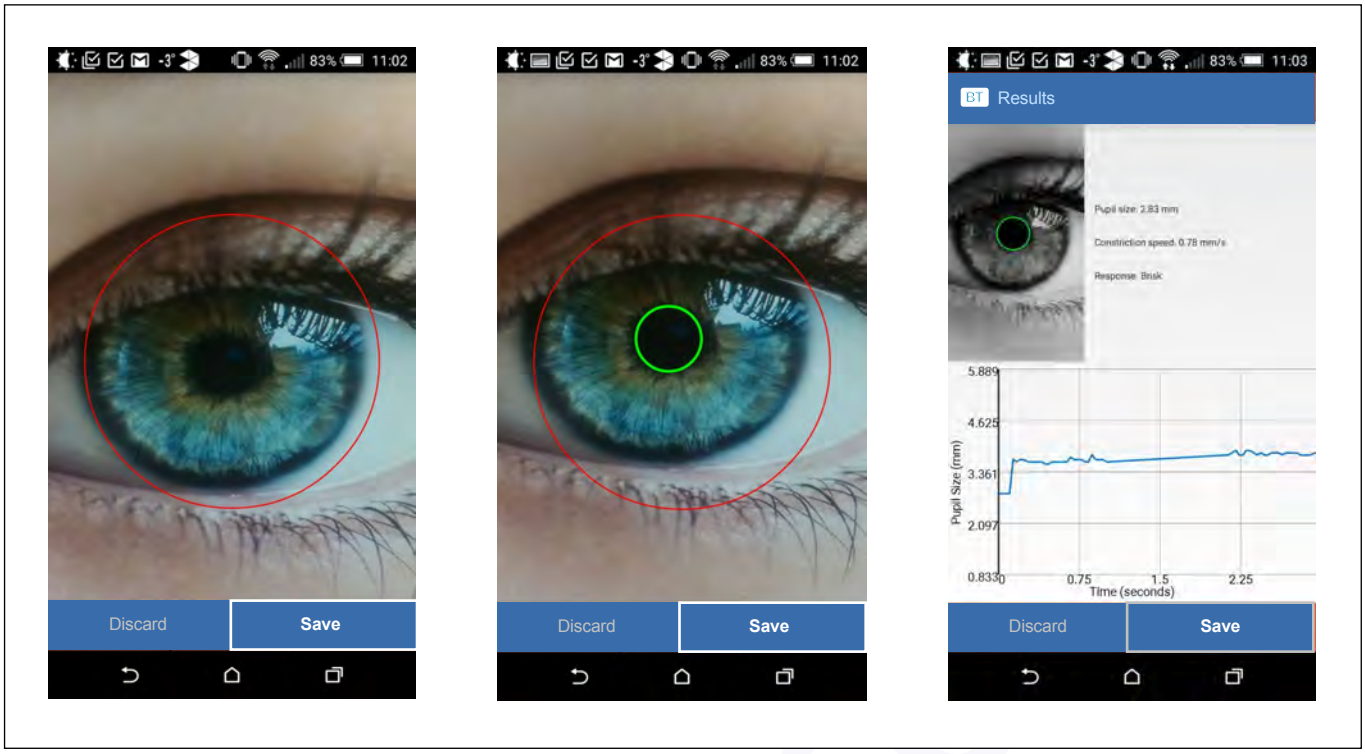


Figure 4: *From left to right: the pupillary light reflex test instruction screen, a patient's iris fitted to the red iris circle, pupil detected during the test, and the results screen from the light reflex test.*

Next, the user will press and hold the button corresponding to the eye of interest. This initiates pupil detection, which finds the pupil and fits a green circle to it, displayed to the user. Once the user is confident that the patient's pupil has been found, the button is released, starting the pupillary light reflex test. This starts a video recording, during which the flash is turned on for one second.

Then the video is processed offline, measuring the size of the pupil in each frame. The constriction speed is measured by comparing the size of the patient's pupil before and after the flash. After processing, a results screen is shown, which displays a video playback of the test and a report of the patient's pupil size and constriction speed (Figure 5). It will also grade the constriction speed as described above. A graph plotting the pupil size over time is also shown in order to provide more feedback to the user.

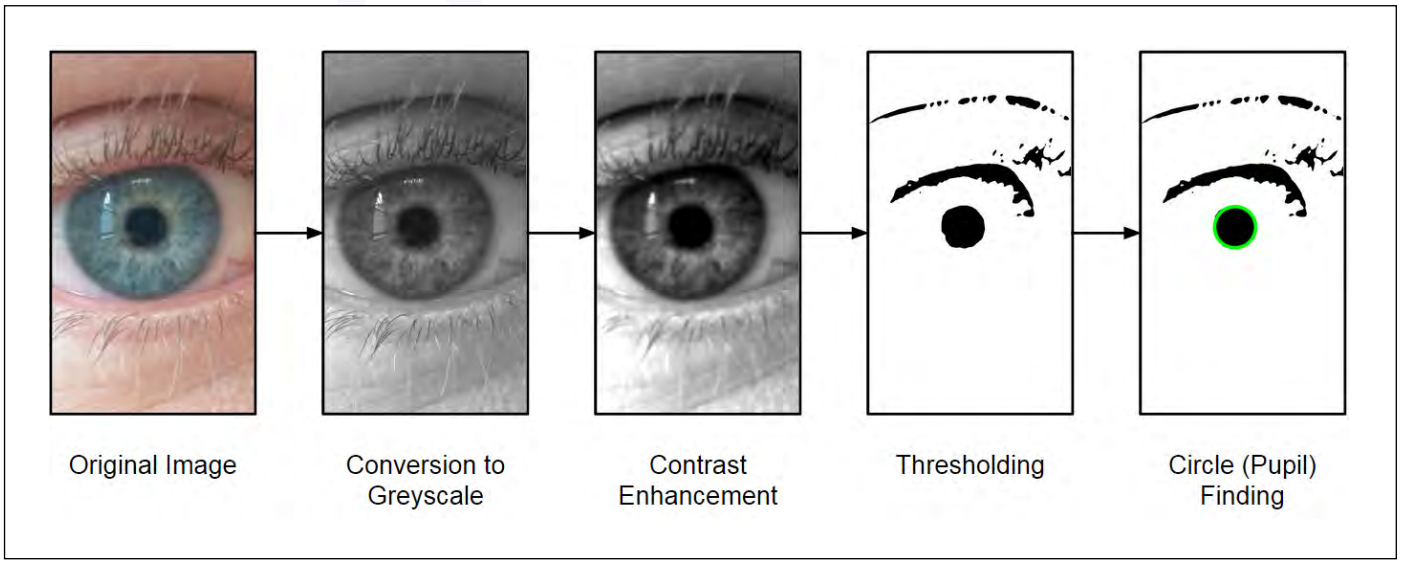


Figure 5: *Image processing technique isolate and finds the pupil in each video frame.*

The pupil detection algorithm used by BT is depicted graphically in Figure 5. The frames recorded by the user's device are first converted to grayscale, stretched in contrast, and then thresholded [14]. The resulting image is then searched for contours, one of which is assumed to be the pupil. The pupil is found by examining the size, position, area, and aspect ratio of each of these contours, knowing that the patient's pupil is circular and should be near the center of the red circle.

PATIENT HISTORY

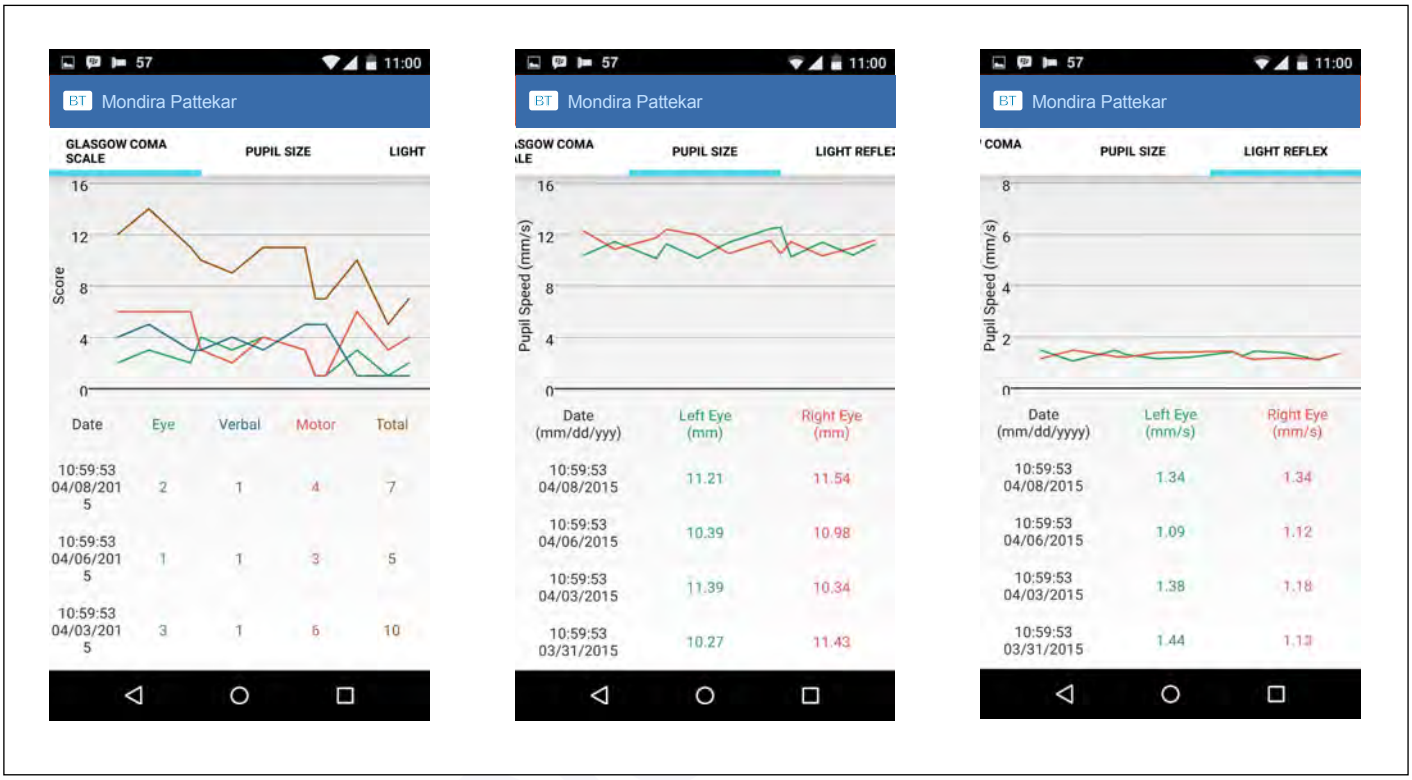


Figure 6: *The patient history screen view past patient test results. These results are graphed over time so that progress can be quickly assessed.*

FUTURE WORK

A. Refine & Perfect Pupil Recognition

Before BT can be reliably used in a hospital setting, its pupil detection algorithm must be improved to the point that it will function even in suboptimal conditions such as poor lighting, or on patients with dark irises. This might necessitate the use of lenses, cameras, or lights that are external to the user's device.

B. Validate Algorithm for Grading Pupil Reactivity

The algorithm for grading pupil reactivity (e.g. brisk, sluggish, absent) is current based on a single policy bulletin paper [5}, therefore further research and testing on patients with neurological disorders or brain injuries is required to strengthen and validate the algorithm.

C. Comprehensive Statistics

BT currently displays past patient results in a simple line graph format, as can be seen in Figure 6. Other data visualization and statistical processing techniques should also be explored in the future, as they may provide the user with more insight regarding the patient's health.

D. Clinical Decision Support

Once the algorithm for grading pupil reactivity becomes more robust, there is great potential for building clinical decision support aids within the app. For example, based on the tracked changes in GCS and pupil reactivity, the app can alert clinicians about critical changes that require additional medical attention and alert the need to notify a physician or the need for a CT scan. This added functionality would be valuable for nurses, nurse practitioners, physicians, and for new learners of the neuroscience field.

E. Secure Hospital Server Integration

Currently, BT stores all test results on the user's device, which would then need to be manually transferred to hospital database servers. An improvement upon this would be to store these test results directly on hospital servers, improving the overall user experience, and also reducing risk of exposing a patient's medical records due to the loss or theft of the user's device.

ENGINEERING PUNCHLIST

Summary: Build an MVP iOS app that can measure pupillary light reflex (PLR) from images recorded by the front camera.

The app does the following:

- *Uses the live video feed from the iPhone's front-facing camera, at 30 or 60 FPS.*
- *Instructs the user to hold the device at a certain distance from their face (and automatically detects whether the distance is correct).*
- *Flashes the screen white to stimulate the eye. This will not be the real method of stimulation yet, only a placeholder effect.*
- *Records the live camera feed for a certain duration (1 - 5 seconds). The stimulation light is only on for the first second or so. These durations will be configurable in the source code.*
- *Analyzes the reaction of the pupil to the light stimulus while the video is being recorded. If it is not possible to do this in real-time, the analysis will happen directly afterwards.*
- *Compute features from the (recorded) video, notably the latency, constriction velocity, constriction amplitude, constriction percentage, and dilation velocity.*
- *Display a graph of the pupil diameter measurements over time.*
- *The app only displays the measurements, it does not analyze them any further (i.e. it does not compare them to a baseline in order to determine whether the pupillary response is regular or abnormal).*
- *Instead of using the live camera, the app can also perform these measurements on one or more pre-recorded videos. (This makes it possible to perform repeatable tests and compare them against known measurements.)*

To measure the diameter of the pupil, the following steps are necessary:

- *Extract the area that contains the eye from the video frame.*
- *Normalize this image region, so that the eye is of the same size in each video frame. We don't want (small) movements of the user towards/away from the camera to be interpreted as the pupil constricting or dilating.*
- *Possibly apply other video stabilization techniques to get reliable measurements.*
- *Segment the pupil from the iris and sclera. This can be done with a neural network or using classical computer vision techniques.*
- *In the segmented image, measure the diameter in pixels and convert this to mm.*

Because light intensity is inversely proportional to the square of the distance from the source, the distance between the user's face and the screen (and camera) is very important. There are two possibilities here:

1. The entire face is visible. This is at a distance of approx. 25 cm or more (10").
2. Only one eye is visible. This is a distance of approx. 15 cm (or 6").

If it is possible to make the entire face visible, the app can use Vision face tracking (on devices older than the iPhone X) or the more detailed ARKit face tracking (on iPhone X or better) to detect where the eyes are. In this case, no new technology needs to be developed for finding the eyes in the video image. Since the face tracker will (roughly) give the location of the eye, we can easily extract this image region for further processing.

Note: As of iOS 13, the built-in face tracking models are supposedly capable of detecting the pupil very accurately (but it's unknown how well this tracks the dilation / constriction of the pupil over a short time span; by itself this API might not be enough to measure

the PLR).

However, these face tracking APIs do not give reliable results when not the entire face is visible, i.e. if the user is too close to the camera. If it is necessary for this app to focus on just a single eye instead of the whole face, we should use a different method for determining where the eye is. One possibility is to train a basic object detection model to specifically look for an eye (or perhaps an iris), and then extract that image region.

Alternatively, the app could direct the user to place their eye inside a specific area of the screen that is always in a fixed location, and the app simply crops that fixed region out of the video. This is the least flexible option, but also the simplest to implement. (There is no way to check whether the user is really following the instructions.)

CHALLENGES

- *The measurements, such as constriction amplitude, are in millimeters (mm). This means the user must hold the camera at the correct distance from their face. Factors that might complicate this are differences in device screen size, camera focal length, etc. This will require some experimentation.*
- *Irises / pupils may be only partially visible as a result of eyelid occlusion.*
- *The user may close their eyes / blink during the recording. The app should detect this and abort if there are too many frames without suitable measurements.*
- *Because the user is holding the camera in their hand, camera movement during the recording is unavoidable. The app must compensate for lateral movement, but also for possible perspective changes from the user moving closer to/further away from the camera.*
- *The app should work well for people with dark irises, thick eyelids, and so on. If we end up training our own neural networks, the collected training data should reflect the wide variety of eye shapes and colors.*

Because there are some unknowns (how to produce the flash) and some of the required technology still needs to be developed (the neural networks), I suggest we start with a basic prototype that is as follows:

- *Implement the UI of the app as described above, including the logic for dealing with the camera, doing the flash, etc.*
- *Use built-in face tracking to find the eye and extract the corresponding image region. OR: if it is already known that the user must be closer than 25 cm (10") to the screen, forego face tracking and use a fixed cropping region.*
- *Use a very basic pupil segmentation algorithm on the extracted image region. This wouldn't use a neural network yet, just thresholding, contrast, contour finding, etc.*
- *Record the measurements and display them to the user.*

This first prototype would not give very reliable results yet, but it provides the foundation; it allows us to swap out the different pieces with improved versions as we develop them.

Once the prototype has been built, we can enhance it in the following ways:

- *Replace the face tracking (or the fixed cropping region) by an eye "object detector". This makes it possible for the user to get much closer to the screen, as we don't need to see the entire face anymore in order to find where the eye is. This could be a Haar detector or a neural network.*
- *Replace the pupil segmentation by a neural network. This model could predict a segmentation mask or perhaps directly output coordinates for the pupil center and its diameter (regression).*

It might be possible to use existing pre-trained neural networks for one or both of these tasks (such as DeepVOG, PupilNet). Often such models are not available for commercial usage, but we can still use them for inspiration.

For the best results, it requires designing and training our own custom neural network(s). This is not something I recommend doing right from the beginning, as it's not clear yet exactly how these would fit into the pipeline. Although I suggest we start collecting training data already.

Training custom detection models requires thousands of training images, with annotations of the true pupil diameter values. In addition, these kinds of annotations should be made for number of test videos, so that the predicted output of the app for these same test videos can be compared to the true values, in order to establish the error rate from the model.

Collecting / acquiring the training data is the expensive part of building your own models, and should not be underestimated! (But is outside the scope of my responsibilities.)

USER EXPERIENCE – FOUNDATIONS

After months of research, we have developed strong ideas about creating a meaningful user experience. Below are questions we asked and preliminary ideas we came up with:

FEASIBILITY

What are the optimal raw physiologic features that can be quality-measured and generated as LIFEdata using mobile smartphones, with a focus on iPhone's optical modality hardware, and smart watches, with a focus on Apple Watch?

- *What conditions or constraints must be in place to ensure quality measures in the form of LIFEdata generation?*
- *How can we reliably measure, extract, process, and make the data available?*
- *Will people allow us to access data via passive and third-party data sources?*

DESIRABILITY

How can we effectively provide Users insights into their body that go beyond current marketplace holistic "wellness" apps while preserving medical and scientific rigor?

- *Whole-body HEALTHscore based on various LIFEdata measurements LIFEdata App v1 users generate*
- *Human body "dashboard" breakdown of the performance of their 10 physiologic systems based on the LIFEdata measures that is known to map to each of these systems.*
- *Individual LIFEdata measures' sub-scores*

What do we have to do to optimize and improve the consumer value proposition that will allow us to reach an installation base of 10,000 users?

How can we most effectively drive engagement to support frequent longitudinal data generation and aggregation?

How and what kind of financial incentives should we build into LIFEdata App v1? For example:

- *Some sort of engagement-based rewards program (i.e., "LIFEpoints")*
- *Potential for redemption for financial incentives.*

How and what kind of educational content should we provide users? For instance

- *Curated health tips and advice*
- *Medical information related to in-App topics*

How can we empower Users?

- *How can we provide them control over their data?*
- *What social features to include?*
- *competition with friends / family around LIFEdata App v1engagement.*
- *Can LIFEdata App v1 include games to engage users and facilitate LIFEdata generation?*
- *Sophisticated design and attractive, informative, and engaging data visualization.*

VIABILITY

- *What gets us to market quickly?*

What constraints exist with respect to LIFEdata App v1 features and functions that Apple permits for the App Store?

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