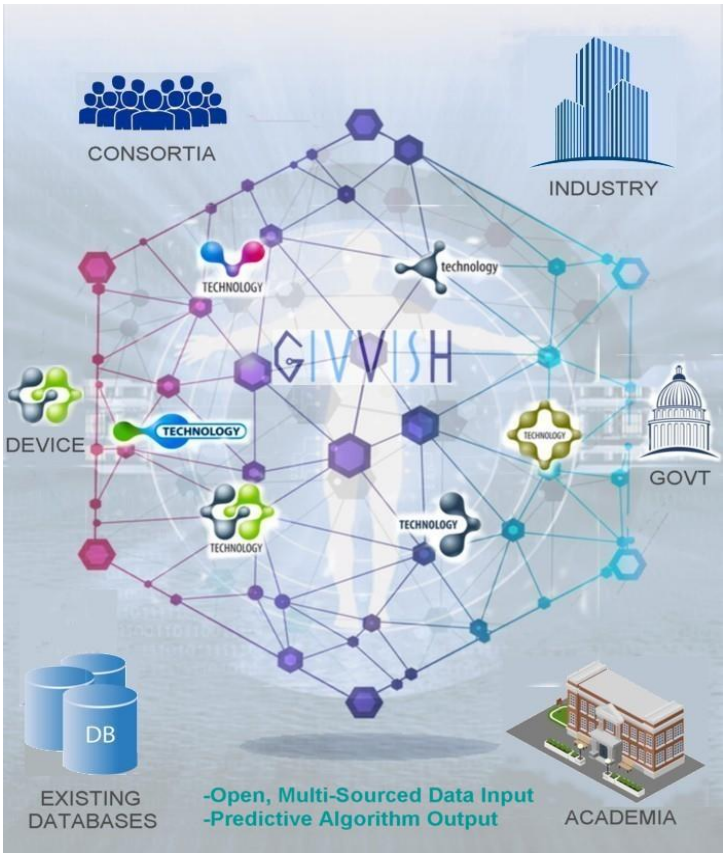
Thank you for inviting public input on the ICCVAM Strategic Roadmap for a National Strategy on new approaches for evaluating safety of chemicals and medical products. The solution to the challenge of achieving a human-relevant predictive model in drug development and toxicity testing would best be accomplished via an actual central and pragmatic project as part of the National Strategy. We need to get away from the idea that everything is so hard to do, just because it is complex. It just takes everyone focused and sharing the discoveries to get it done. We only have to look at other industries and see how they evolve and keep pace with emerging technologies. A good example is the driverless car which became legal in various states a few years ago in 2014. After a period of great skepticism, the entire industry and most of the public is now all geared up for them to be everywhere. How did that happen? Well, a pretty solid safety record. It all started with an industry-wide challenge. A computational model emerged, was tested, and was followed by acceptance by the NHTSA. We can do the same thing.

I'd like to share an idea called GIVVISH. GIVVISH is a functional design and IT platform incorporating a validation mechanism that utilizes the power of "Big Data" and bottom-up collaboration to achieve a predictive, human-relevant model in 3-7 years, replacing the animal model with a new Gold Standard that fits the 21st century. I realize that's a lot faster that what is usually discussed, but timelines are often a function of how many people are involved on a project and GIVVSH involves everyone in the solution. Everyone is a collaborator. The GIVVISH platform (Global In Vitro Validation In Silico Human) is outlined in detail at GIVVISH.org. It would function in real-time, be a non-profit public service platform, featuring an interactive method validation mechanism and library for sharing, analyzing, extracting data, and obtaining predictive algorithms for computational-assisted method validation. It's both a mathematical model and a peer-to-peer platform. The design features user-level security/sharing, a review process, machine learning and continual feedback and optimization. The goal of the platform is to provide a surface and structure for enabling industry, academia, government, and regulatory components to engage in real-time with statistically significant volumes of human-relevant data, to accelerate method validation for these innovative technologies.

This project is in pre-funding stage and we are currently interested in building our Founding Board of Advisors and advancing the design to the next level. The expertise of everyone working on this important topic is needed and appreciated. The GIVVISH vision is a human-predictive model that will help deliver safer, more efficacious therapies, spur innovation, reduce cost, and align with our highest scientific and ethical potential. For a detailed overview of the GIVVISH project, please visit our website at GIVVISH.org

GIVVISH

GLOBAL IN VITRO VALIDATION IN SILICO HUMAN

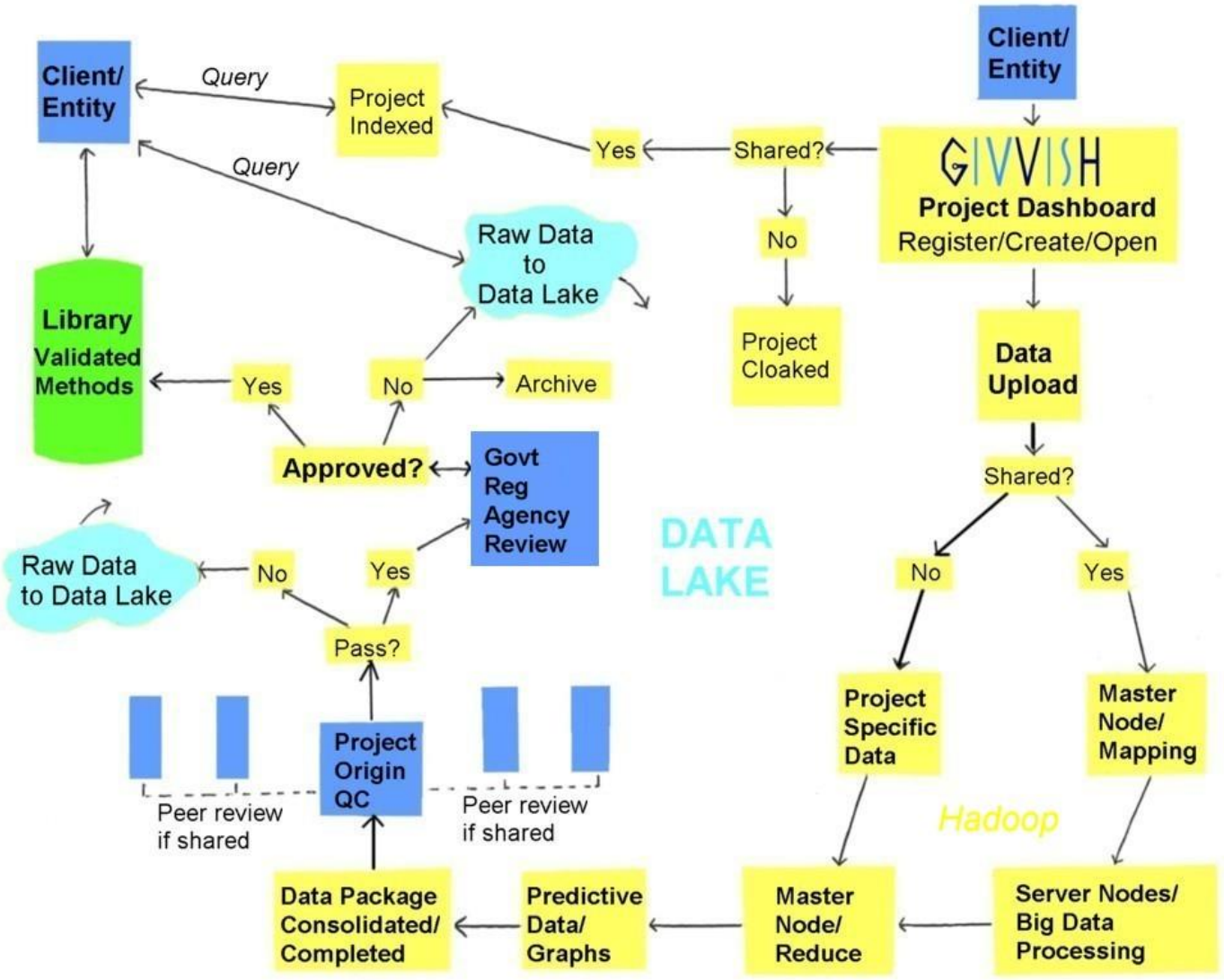


GIVVISH is a proposed collaborative public service project that aims to design, develop, deploy, and maintain a socially-scaled human-relevant method validation platform and library. It will utilize an open-sourced data storage and processing program for delivering super-computed algorithms for supporting evaluation and regulatory-approval of emerging human-relevant methods and tools used in drug development. The platform will feature user/enterprise level security and sharing settings, and a peer review process to streamline the validation pathway for new technologies. In collaboration with industry, academia, and government entities, our goal is to provide the surface and structure needed to organize and review large volumes of data to facilitate the bridge from last century's framework to a 21st century solution- a predictive model based on human biology for assessing human clinical outcome.

Platform design outline-

- GIVVISH will be an end-user, scientific community collaborative project, designed and launched with leading experts in IT, biotechnology, pharmaceutical, academia, government and regulatory agencies for the purpose of creating a centralized and working platform for accelerating validation of human-relevant methods
- GIVVISH aims to seek funding/collaboration primarily via a CRADA (Cooperative Research and Development Agreement) as well as from other interested parties and will function as non-profit public service platform.
- The platform will be a socially-scaled, super-computing platform for data upload, sharing, generation, and predictive modeling of both wet (in-vitro) and dry (in-silico) human-relevant data (i.e. 2-D, 3-D tissue systems, organ on chip, etc).
- Platform will incorporate intuitive design and state-of-the-art machine learning capabilities to analyze data in real-time for statistically significant modeling that continually updates and refreshes code and data sets.
- Hadoop configuration enables wide variety of end-user and enterprise data formats for straight-forward, minimal-programming interface for upload of both historical and newly-generated data
- Configuration will feature user level (or enterprise-level) security and sharing settings for user-defined data-sharing parameters; all shared data will be viewable by authenticated users based on user sharing settings
- All platform data will be viewable by regulatory agencies to enable deep-learning and expedite approval process

- Authenticated Individual researchers, groups, and/or companies will be able to register a profile to utilize the platform; government and regulatory agencies will have full access to all components of platform as well as forum to provide guidance/feedback to project team and platform users toward iterations for streamlining validation process.
- Users will be able to create a new project, open an existing project, and/or compete on a project.
- Users may register/open an endpoint, biomarker, therapeutic candidate, compound, drug entity, target organ, or disease condition for viewing data, uploading data, and extracting data for predictive modeling.
- Platform will produce data sets, charts, graphs and other visual representations of data at all levels of input and analysis and include social feature with peer review, interpretation, and feedback, based on user sharing/security settings.
- Data will conform to electronic records regulatory and GLP requirements as applicable.
- Regulatory agency is final arbiter of validation approvals.
- All shared data in Data Lake will be available to platform users for query.
- Existing validated methods as well as platform-generated validated methods will be available on platform library for query.

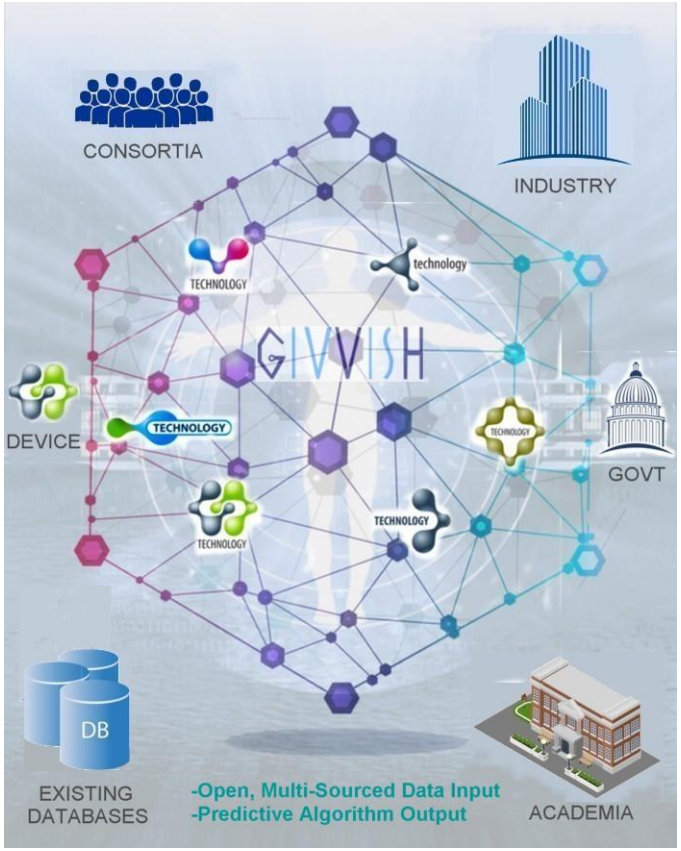


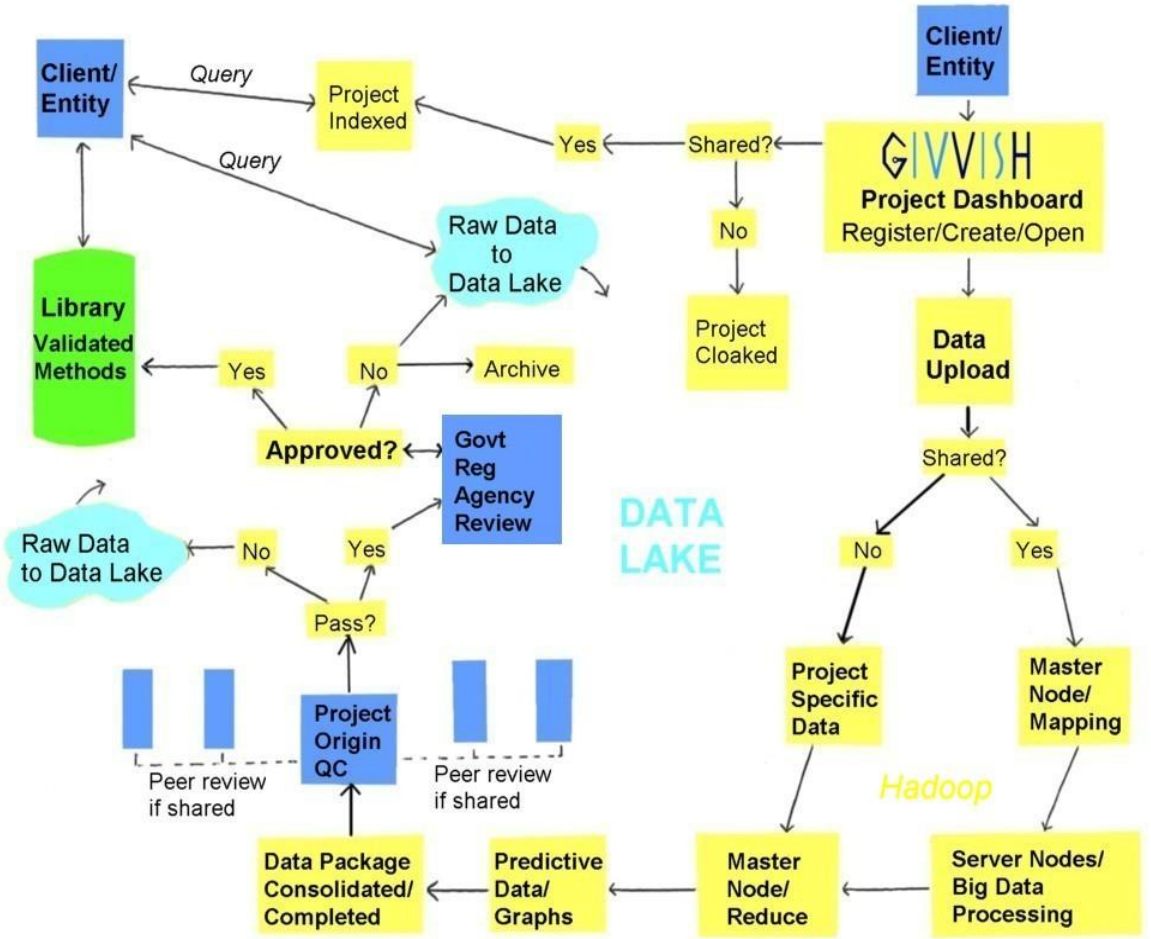
Streamlining Validation of Human Relevant Methods utilizing "Big Data"

For more information, please contact: info@givvish.org

GIVVISH

GLOBAL IN VITRO VALIDATION IN SILICO HUMAN





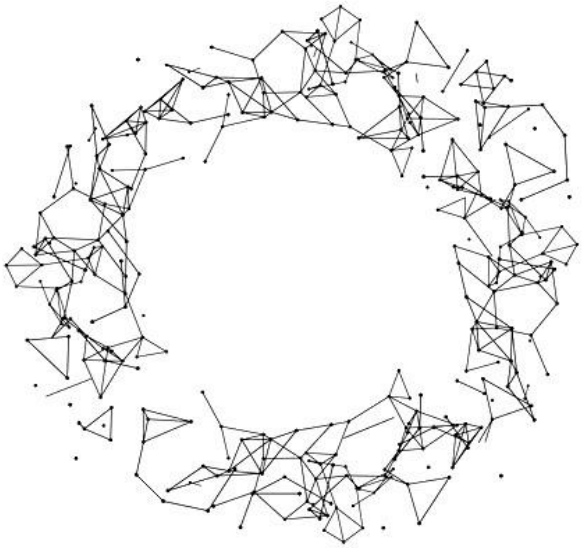
Streamlining Validation of Human Relevant Methods utilizing "Big Data"

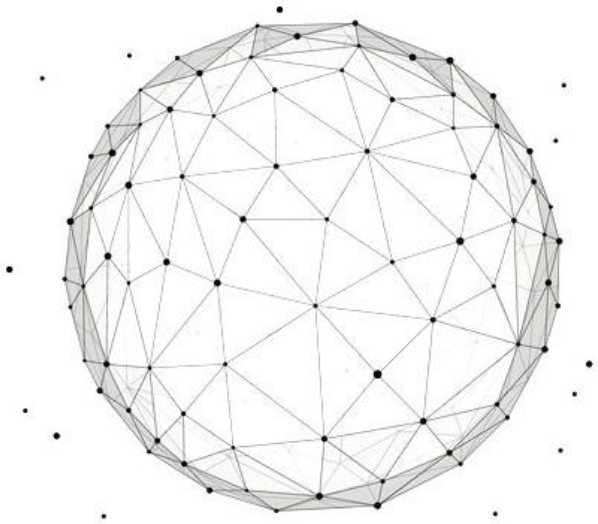
- 21st century solution powered by Hadoop
- Socially-scaled for large volume of data
- Logical path to predictive model
- Data & Projects organized and accessible

- Validation parameters straight-forward
- Easy flow of collaboration
- Generates Library: existing & new approved methods
- Resource-friendly
- Progresses innovation

- Shortens learning curve
- User/Enterprise level sharing/security settings
- Human-relevant tools mainstreamed
- Harmonizes existing efforts
- Economic boon for industry

HUMAN RELEVANT METHODS: CURRENT VS FUTURE STATE





CURRENT STATE

-Projects and data isolated & unorganized

-No central library of validated methods

-Subject matter experts few and isolated

-Human-relevant tools widely unknown

-Volume of data required out of reach

-Regulatory path unclear

-Cutting-edge technologies languishing

-Validation parameters confusing

- 21st century IT capabilities untapped

- Observational to predictive model skewed

-Drug discovery resource-intensive

-Opportunities for collaboration efforted

-Slow pace of on-boarding knowledge

-Industry is in economic stall

FUTURE STATE/ GIVVISH

-Projects and data organized and accessible

-Library of validated methods; existing & new

-Subject matter socialized for participation

-Human Relevant tools mainstreamed

-"Big Data" enabled and plentiful

-Regulatory path supported

-Innovation spurred

-Validation parameters straight-forward

-Alignment with today's IT capabilities

-Logical path to predictive model unfolds

-Process streamlined/economical

-Easy flow of collaboration

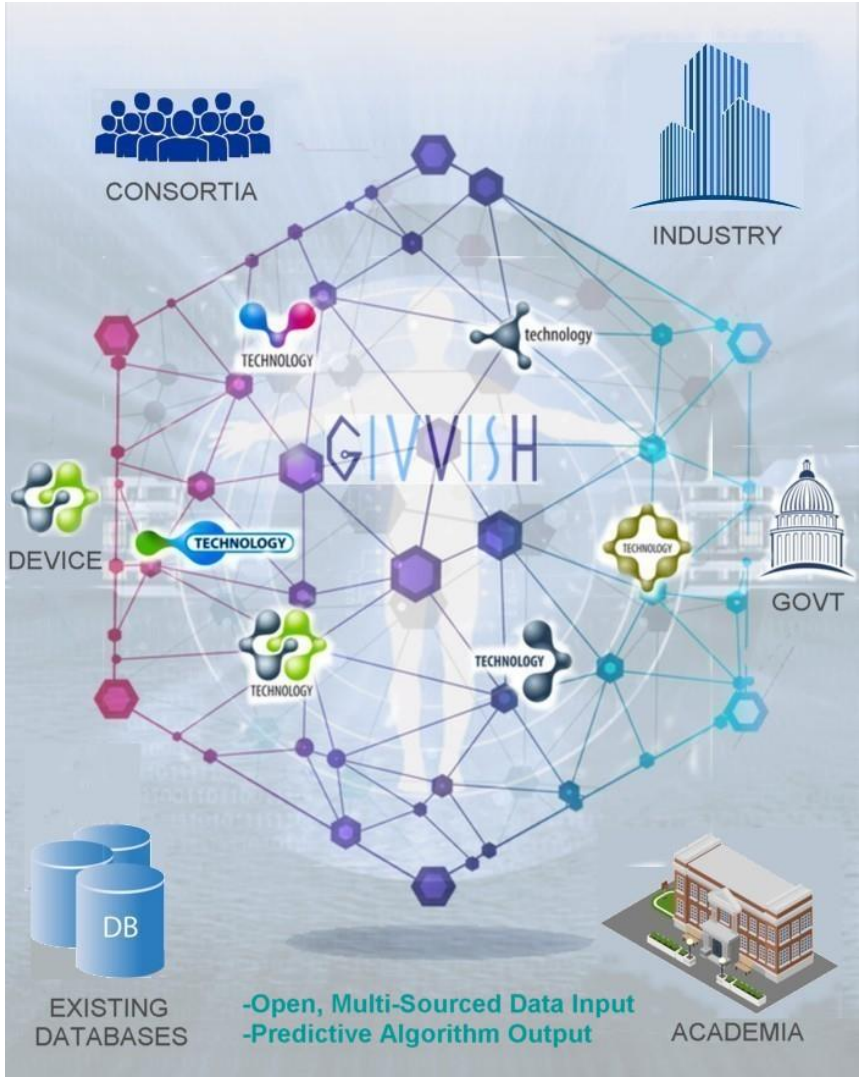
-Structure supports education of technology

-Economic boon with catapult to 21st century

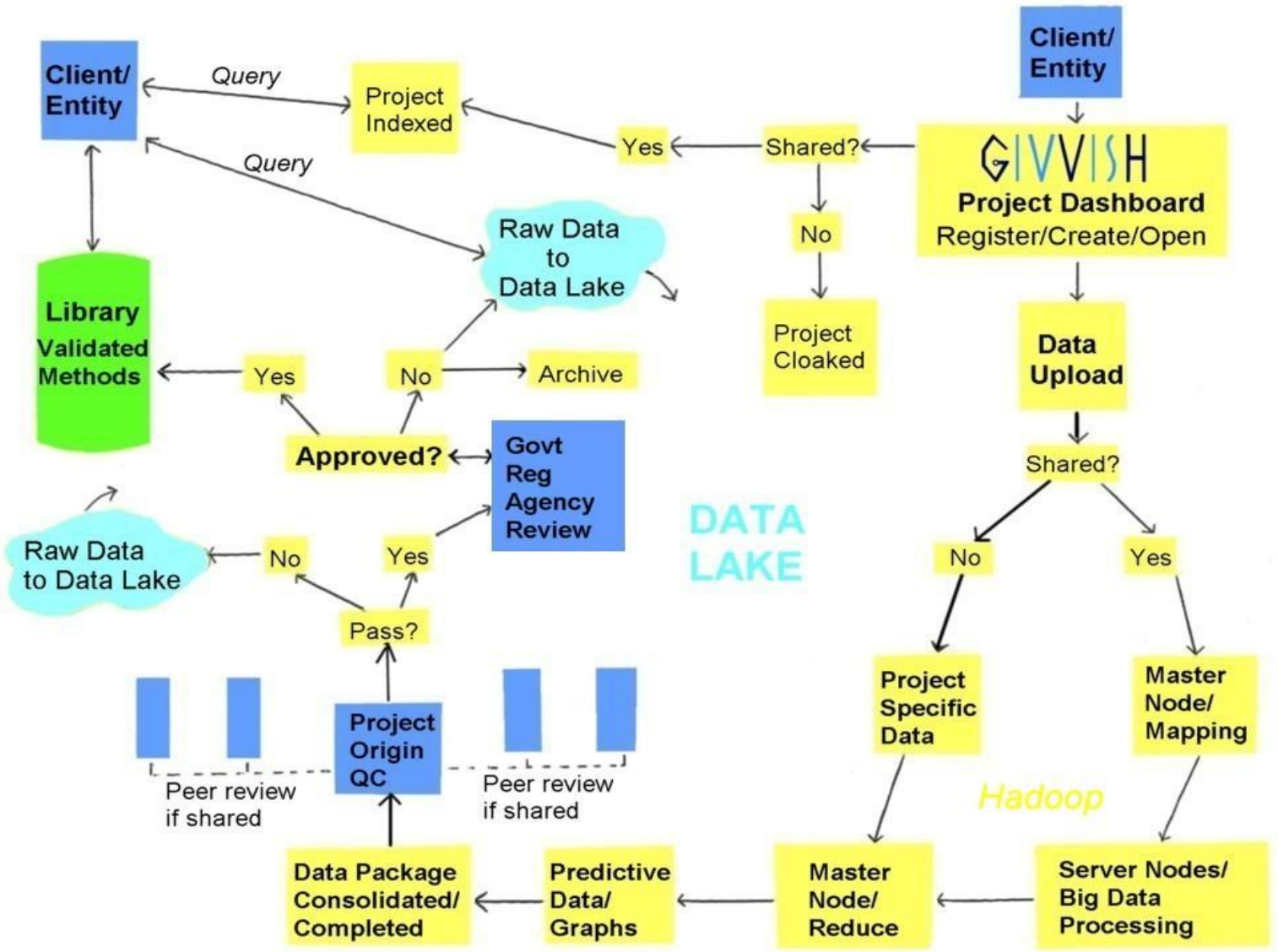
GLOBAL IN VITRO VALIDATION IN SILICO HUMAN

OVERVIEW OF VALIDATION MECHANISM & THE USER EXPERIENCE

KEY FEATURES OF PLATFORM



- BOTTOM UP BUILD
- BIG DATA with REALTIME PROCESSING
- SOCIALIZES THE DATA, THE HUMAN RELEVANT CHALLENGE & THE SOLUTION
- USER-LEVEL (ENTERPRISE LEVEL) SECURITY/SHARING
- COLLABORATIVE
- PEER REVIEW
- CENTRALIZES LIBRARY OF EXISTING VALIDATED METHODS
- ORGANIC VALIDATION MECHANISM
- ORGANIZES DATA/MERGES NEW DATA
- SUPPORTS EDUCATION/ NATURAL LEARNING CURVE
- SUPPORTS REGULATORY DECISION BURDENS
- FEEDBACK MECHANISM TO ALL STAKEHOLDERS
- CENTRALIZES COMMUNICATION
- INFINTE DATA SEARCH CAPABILITIES
- RESEARCH TOOL



Streamlining Validation of Human Relevant Methods utilizing "Big Data"

DATA INPUT ORIGINS:

- INDUSTRY
- GOVERNMENT
- ACADEMIA
- DEVICE MAKERS
- CONSORTIA
- EXISTING DATABASES
- CLINICAL TRIALS
- HISTORICAL DATA

OUTPUTS:

- CALCULATIONS
- PROBABILITY PLOTS
- DIAGNOSTICS (R, R-sq, p-value, AIC, BIC, etc)
- CORRGRAMS
- ANOVA
- SUMMARY

AGENDA- OVERVIEW OF VALIDATION MECHANISM

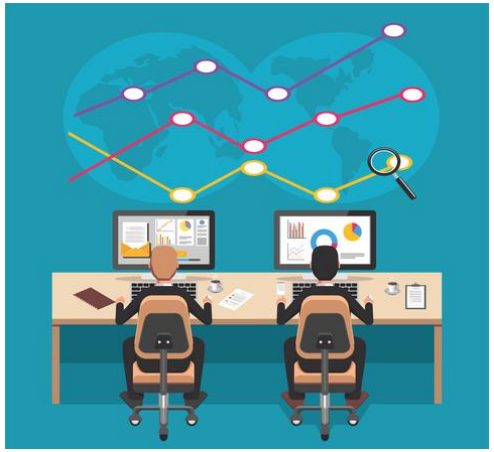
- DESIGN
- SYSTEM REQUIREMENTS
- USER PROFILE
- SECURITY/SHARING
- SEARCH
- PROJECTS
- MAPPING
- REDUCE
- DATA PACKAGE
- SUMMARY
- PEER REVIEW
- VALIDATION SUBMISSION
- APPROVAL PROCESS
- ARCHIVES
- LIBRARY
- DATA LAKE

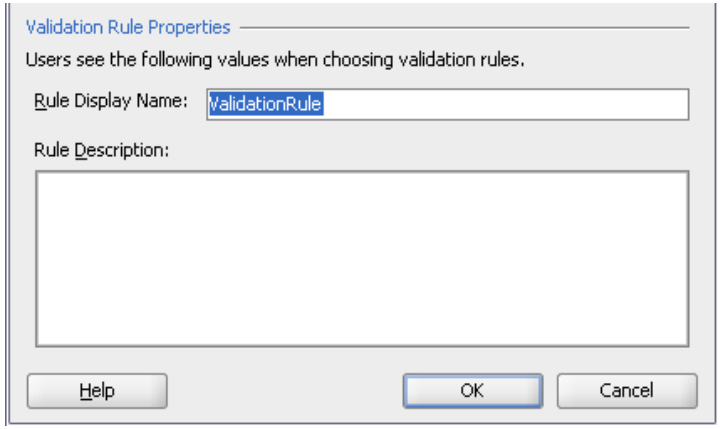
GIVVISH
GLOBAL IN VITRO VALIDATION IN SILICO HUMAN

GIVVISH DESIGN & SYSTEM

- Physical location for Hardware /servers
- Open-source with Hadoop Processing/assisted by MapReduce, Hive, Spark, etc
- Real-time computing/Machine Learning
- User-Friendly with minimal end-user programming for data upload
- Adjustable configuration (i.e. Validation Parameters, Security)
- GLP compliant
- Optimization for Quality Assurance

Hadoop





USER PROFILE & SECURITY/SHARING

The User Profile and Security/Sharing settings:

- One of the primary drivers of platform use/success
- User authentication
- Users can find and connect to team members, collaboration partners, and build/assign project teams
- For enterprise users, enterprise level security will likely define security/sharing options for the user during authentication.

GIVVISH

- a POWERFUL TOOL in the BIG DATA setting

Users will be able to search the Data Lake for raw data, view and open shared projects, archived projects, validated methods library, or conduct keyword search.

Data from search can then be extrapolated and further manipulated for research, hypothesis testing, critical analysis, variance analysis, etc.

PROJECTS

- Search
- Open
- Create New

Projects are the basic building blocks of the platform and are associated with user/user teams.

Projects can be uploaded, viewed, competed on, or interacted with based on sharing settings.

- Endpoint
- Biomarker
- Therapeutic Candidate
- Drug/API
- Target Organ
- Disease Condition

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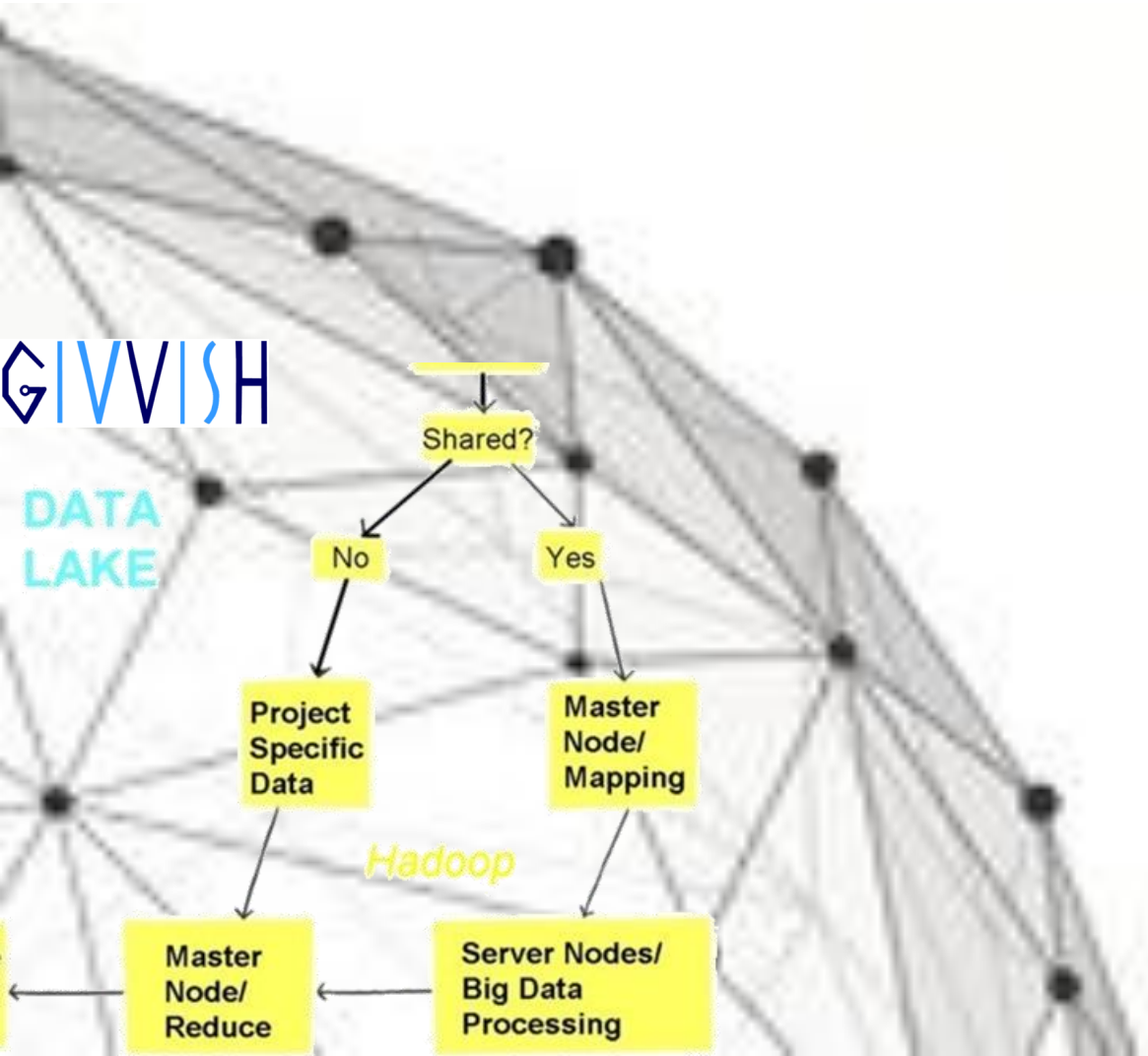
MAPPING & REDUCING- Big Data's Wheelhouse



MAPPING- Program will map the project data to distributed server nodes on the platform for processing/analysis.

REDUCING- Computed data will then be reduced/consolidated at Master Node for outputs and returned to project origin team for QC.

*For shared projects, a second set of reference data will be returned that is cumulative with any statistically-significant related data in Data Lake, along with correlation- probability data.

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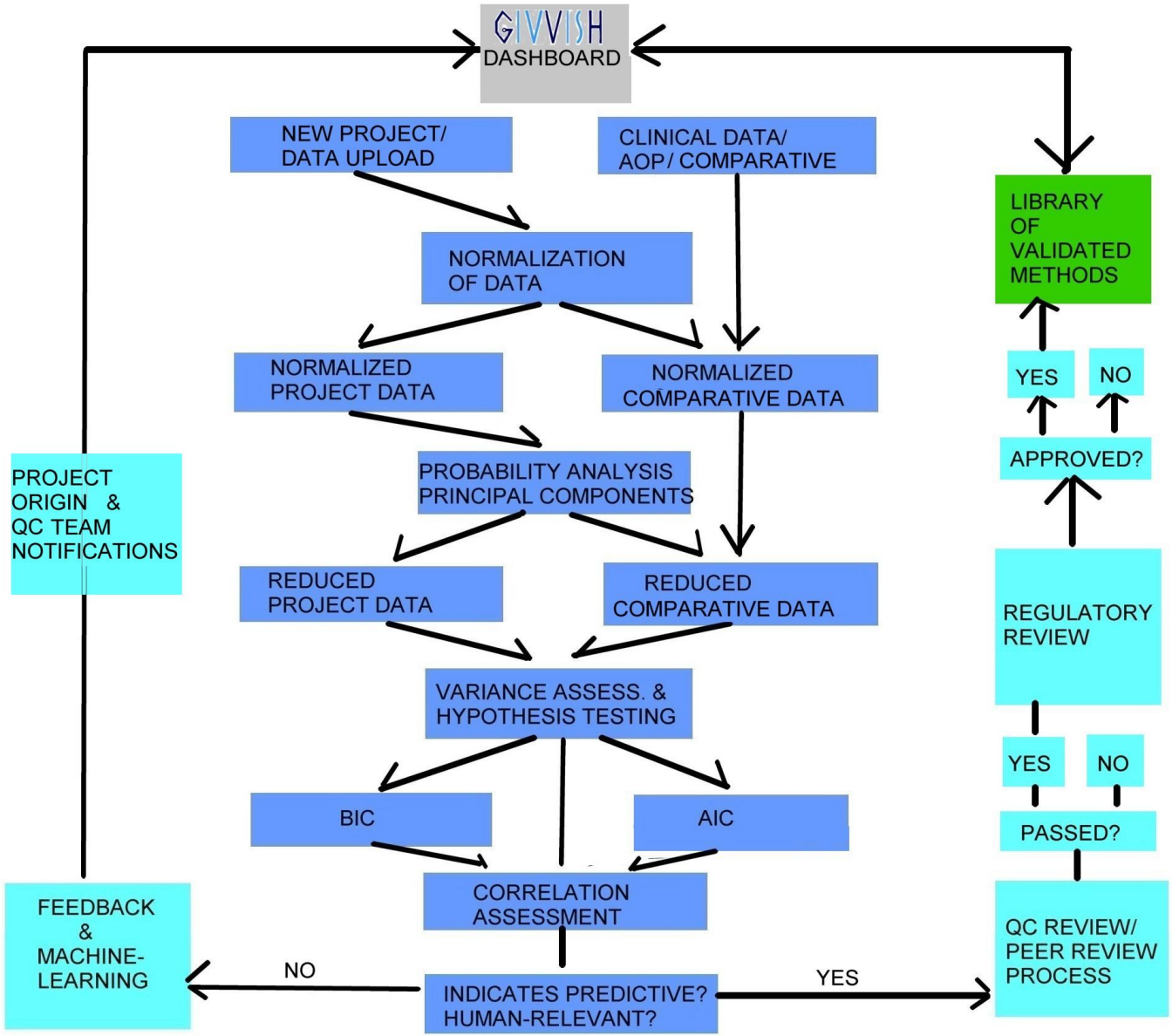
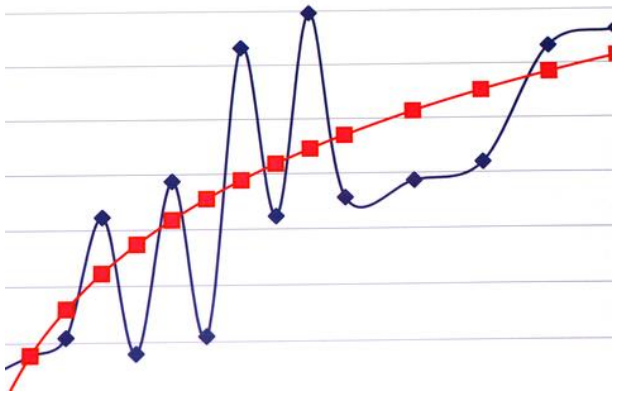
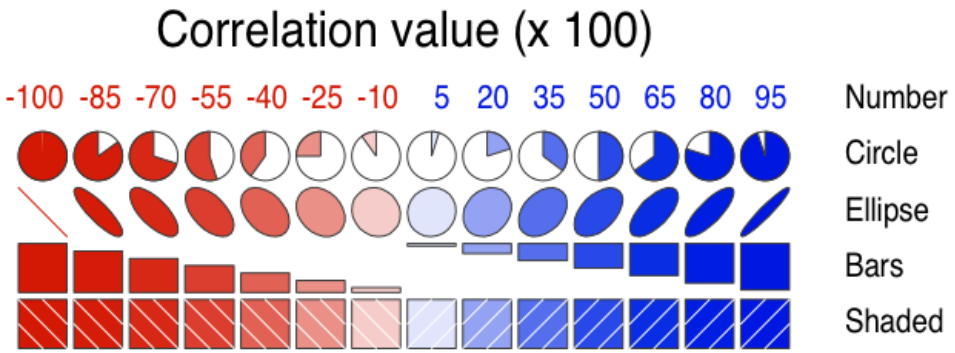
HUMAN-RELEVANT METHOD VALIDATION



Data Package and Summary





- ✓ Data returned from processing will include calculations from project as well as a set of cumulative calculations if shared.
- ✓ Outputs will also include visual representations of the data such as histograms, charts, probability plots and corrgrams (if multivariate data).
- ✓ Captures Diagnostics: R-Sq, p-value, AIC, BIC, for analysis of variance and comparative modeling.
- ✓ A summary will also be generated.

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Data Package and Summary (cont.)

- ✓ examines influential observations and calculates accuracy
- ✓ Performs k-fold cross validation and capture mean-squared error for model

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PEER REVIEW & VALIDATION SUBMISSION

The Peer Review Process:

- Dependent on project sharing settings
- Recommended approach- enhances confidence and provides collaborative learning
- Project Origin QC team initiates the Peer Review process
- Selected reviewers receive a dashboard notification that a project is ready for review
- Project Origin team decides whether to pursue or halt validation
- If advancing as validation candidate, project is submitted to Regulatory Agency for review
- Any projects not advancing are returned to Data Lake in raw data form; the computed data is also archived in project form for future retrieval

GIVVISH

VALIDATION APPROVAL PROCESS

- All projects submitted for validation must have sufficiently met acceptance criteria and validation parameters.

- In Regulatory Review, establishment/correlation of human relevancy may undergo supercharged review as the Regulatory Agency has access to ALL platform data. This provides extensive search and computational support in decision-making.

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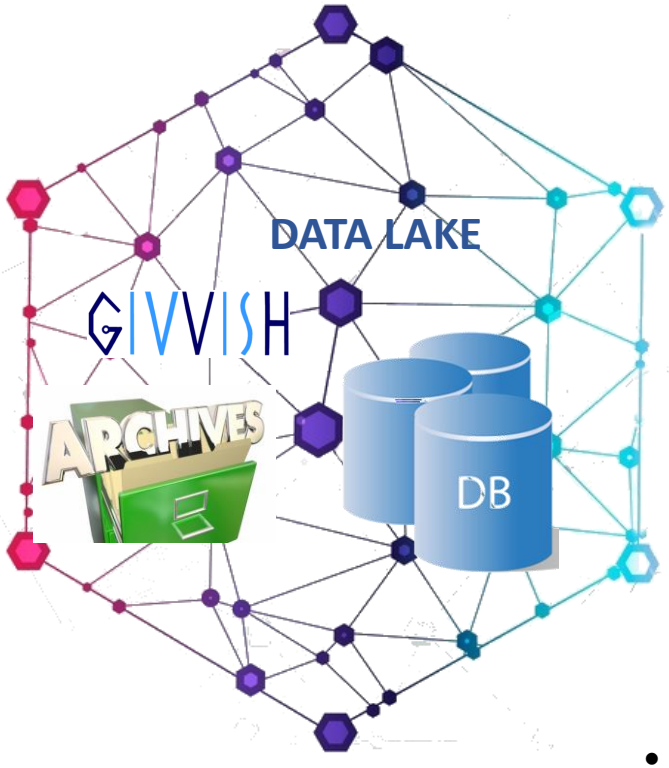
ARCHIVES, LIBRARY & DATA LAKE



DATA LAKE

- Raw and associated data in any format
- Data in Motion

ARCHIVES

- Stored project- specific data
- Data-at-Rest

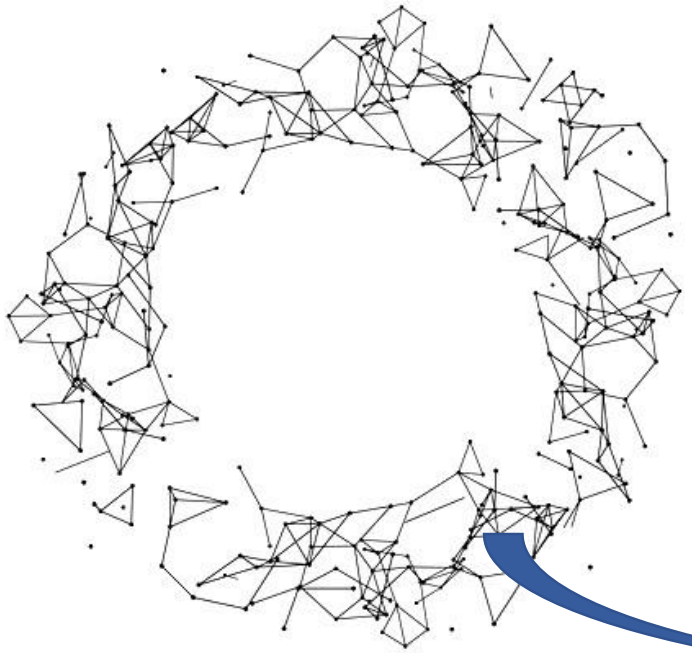
LIBRARY

- Validated Methods Library
- Historical data
- May be in-Motion or at- Rest

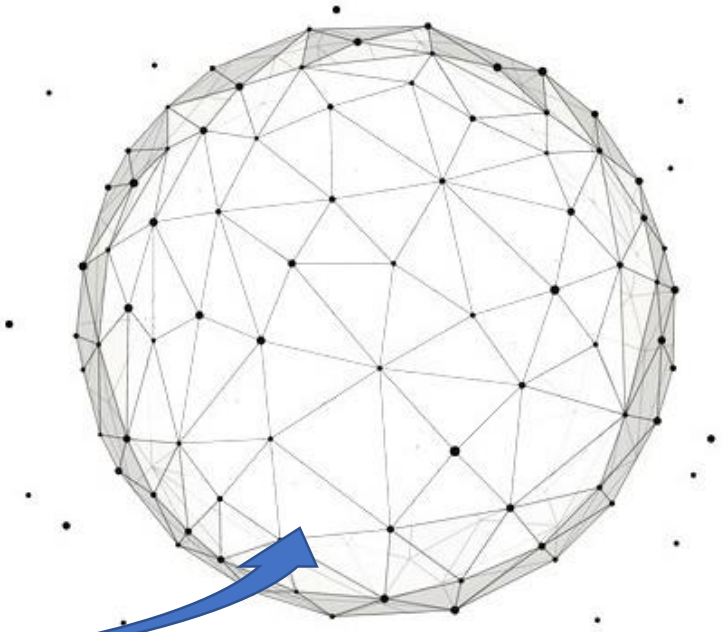
THE USER EXPERIENCE

GIVVISH

THE USER IS CELEBRATED



- ✓ DISCOVER
- ✓ OBSERVE
- ✓ CORRELATE
- ✓ CONFIRM



SHARING

THE USER EXPERIENCE- INTERACTIVE & DYNAMIC

The user is a collaborator. What can users do? Everything.

- ✓ Search and View any shared data and projects
- ✓ Open and Create New projects and upload data
- ✓ Research, Compute, and Extrapolate data and reports
- ✓ Create and perform Optimization Studies
- ✓ Perform Hypothesis Testing
- ✓ Create Statistical Reports against any searchable criteria
- ✓ Assess Method Performance against any searchable criteria
- ✓ Peer Review projects and provide feedback
- ✓ Communicate with other platform users
- ✓ Perform Trend Analysis on Validated Methods Life Cycle
- ✓ Conduct Method Comparability Studies
- ✓ Provide feedback on DOE (Design of Experiments)

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MILESTONE TIMELINES

GIVVISH

1-9 months	< 1 yr	1-3 years	3-7 years
Advisory team and IT to liaise on detailed design; requirements	Current Validated Methods uploaded	On-boarding across all user types and data types	Widespread adoption across industry as Validation Library Grows
Location for field installation of hardware identified	Historical data loaded/ incl Clinical	Continual Optimization Studies of Model with feedback mechanisms	Statistical Power & Range increases with wide use/ supercharging Robustness
Software/hardware Development; Field installation	Databases loaded in all formats/ Library available for search	Platform officially launched for Validation process	High confidence in Human Relevant models achieved as confirmed clinically
Communication plan; Early adopters identified	On-boarding of early adopters	Continual Method Performance; Devices become more refined	Platform begins to also become a Clinical Research Tool for all phases
	Beta Testing	Platform begins to correlate and predict/ initial Methods Validated	Human-Relevant Predictive model replaces animal models; A new Gold Standard emerges

GIVVISH

GLOBAL IN VITRO VALIDATION IN SILICO HUMAN

Thank You!

Contact:
info@GIVVISH.org