Leveraging Real-World Data in Rare Diseases: Longitudinal Data Sets as “Virtual Natural History”

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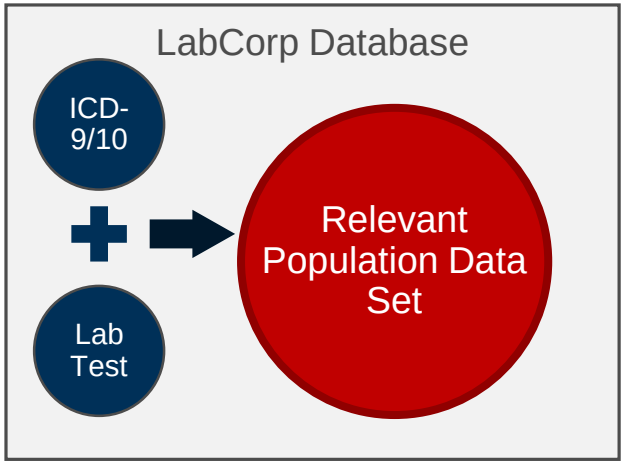
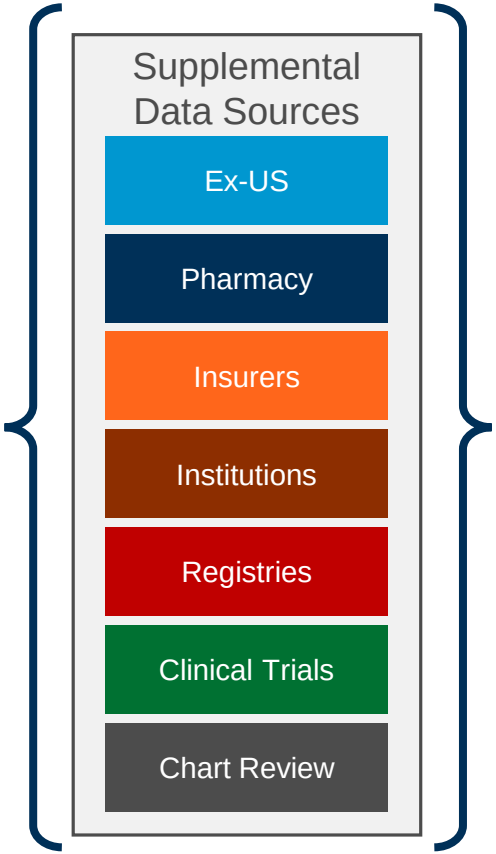
Data Set Development



Foundational Longitudinal Data Set



Supplement & Expand Dataset

Anonymized Longitudinal Data Set

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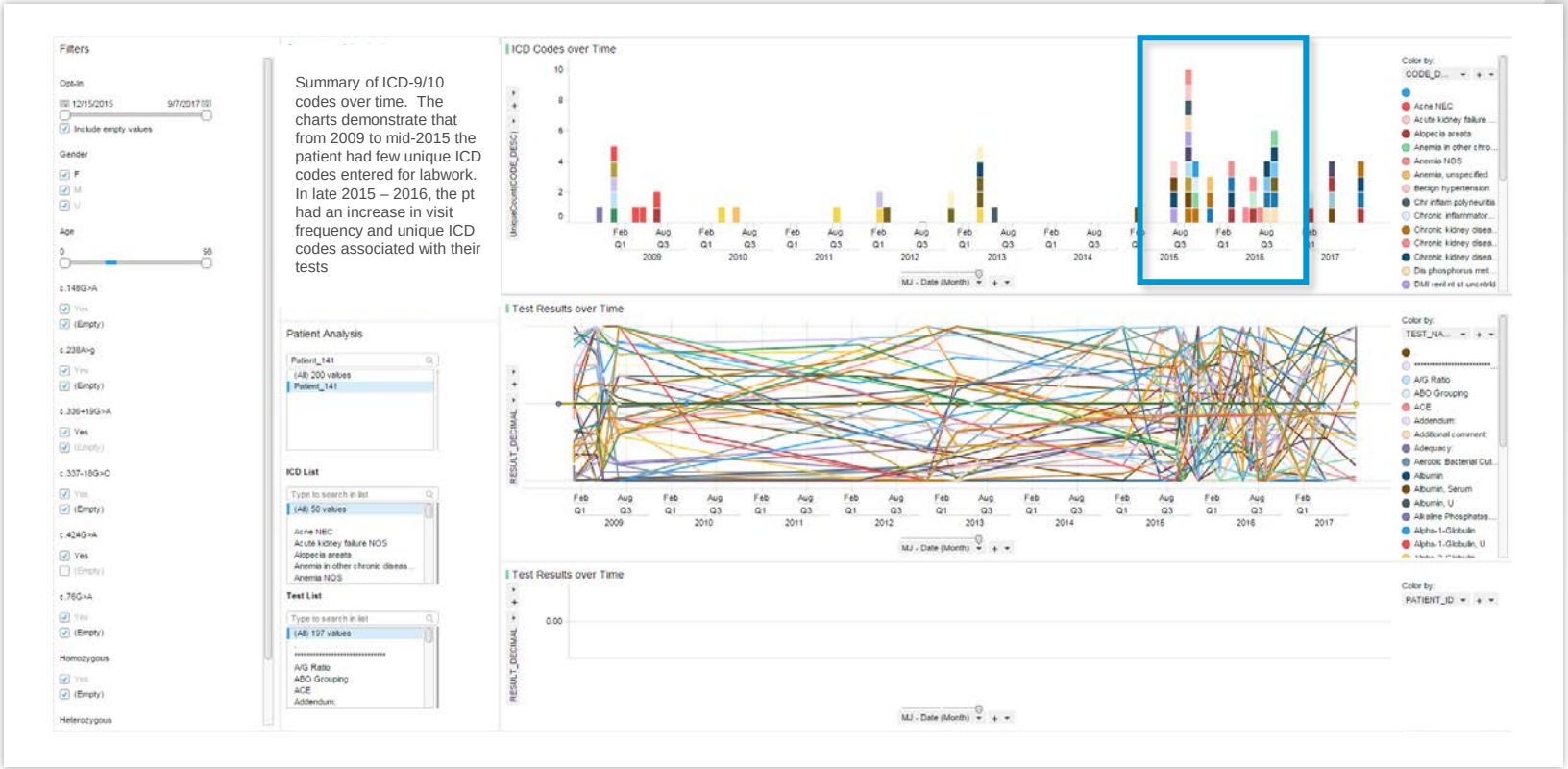
Longitudinal Results for a Single c.424g>a Patient



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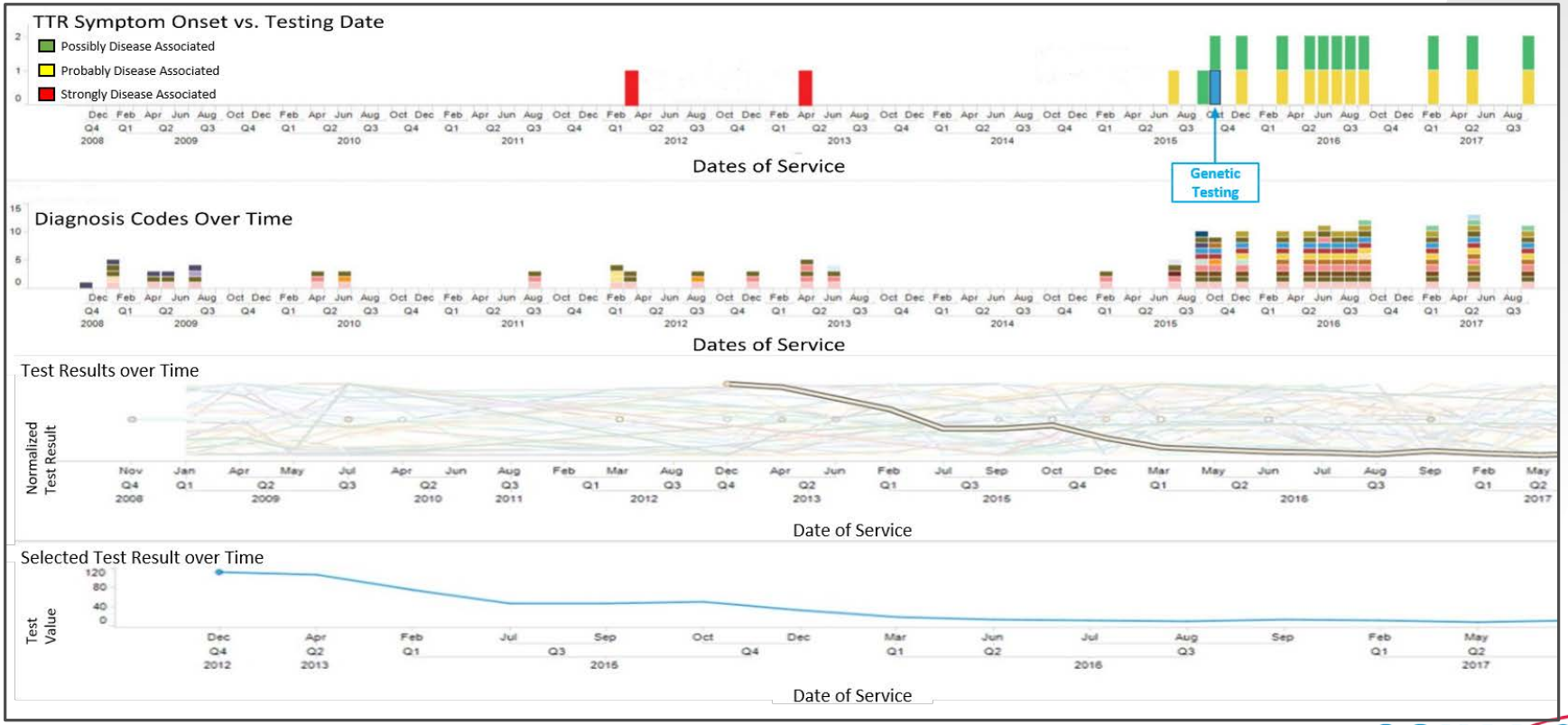
Longitudinal RW Data - Individual Patient

aTTR Patient with c.424G>A



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Genotype-Phenotype Insights

- Amyloidosis
- Cardiac
- Neuropathy
- Renal
- Fatigue

1. http://amyloidosismutations.com/mut-attr.ph
2. https://www.ncbi.nlm.nih.gov/clinvar/variation

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Impact of I/E Criteria on Patient Pool

26% Reduction in Eligible Patients

853	Patients between 10/2010 and 10/2018 with transthyretin variant by genotyping
801	Patients between 18 and 82 years old.
796	Without HIV, Hep B, Hep C
787	Without Malignancy, Autoimmune disease, or other neuropathy
786	Without primary amyloidosis
776	Without liver transplant
642	With creatinine < 6 mL/min/1.75
635	With Platelets < 125 x 10^9L
627	With ALT and AST > 1.9 ULN

The protocol inclusion / exclusion criteria is applied to the patient pool and then matching patients are geo-located on the map.

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Longitudinal Data as a Control

Retrospective “Synthetic” Control Arm

- Integrate historical past clinical trial datasets: Covance Labs, Sponsor clinical data (EDC)

Retrospective “Contemporary” Control Arm Study using RWE

- Integrate real-world datasets, identify patients in historical RWD who meet study criteria
- Outcome analysis to:
  - Define an index event (e.g., start of control treatment)
  - Define the observation period
- Analyze outcome (incidence rates, Kaplan-Meier analysis, etc.)

Prospective “Synthetic” Control Arm Study

- Collect study data, including direct from patient through surveys, ePRO, mHealth apps
- Integrate direct from patient data with EHR / Labs and other data sets for analysis

Real-World Comparative Safety Study

- Compare adverse events (AEs) rate of lab testing and clinical outcomes determined by diagnosis codes of Product X to the rate experienced by currently available products

Real-World Evidence: Bridging the Gaps

- Unbiased by trial selection/recruitment process
- Leverages multiple, existing data sources
  - More robust, more rapid
  - Potential to unify fragmented data
- Enables identification / diagnosis of target population
  - Characterize the patient journey
- More effectively characterize genotype-phenotype
- Hypothesis test
- Protocol modeling

Back-up

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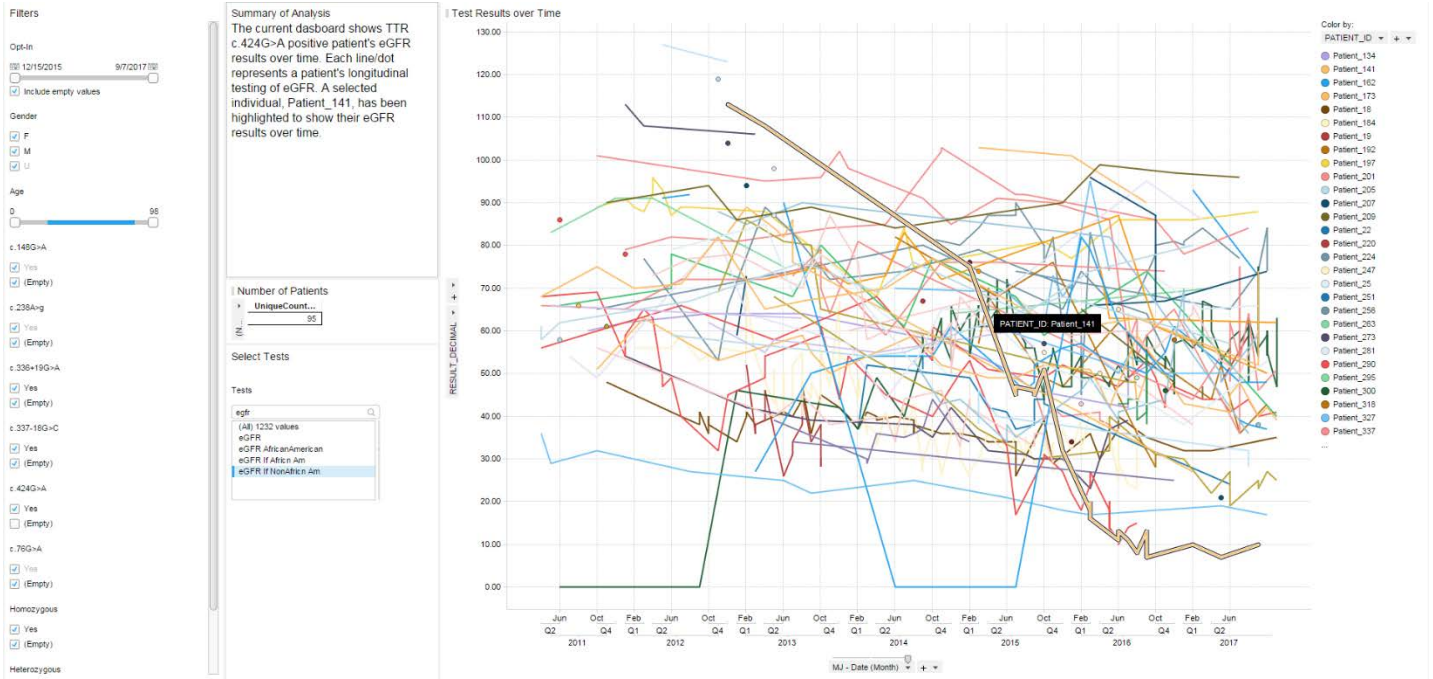
“Virtual Natural Histories” – Longitudinal RW Datasets

Longitudinal eGFR results for c.424g>a aTTR patients



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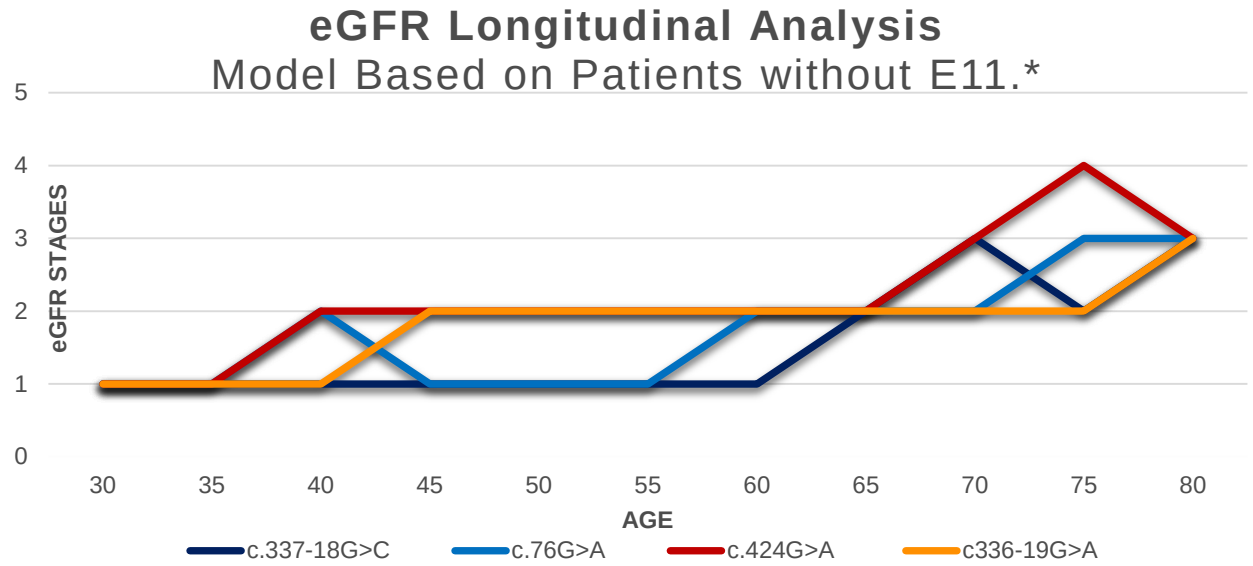
Exploring Predictive Modeling: eGFR & Age by Mutation



Stage	Kidney Disease	GFR
1	Normal	> 90 mL/min
2	Mild CKD	= 60-89 mL/min
3	Moderate CKD	= 30-59 mL/min
4	Severe CKD	= 15-29 mL/min
5	End Stage CKD	<15 mL/min

Mutation type	c.337-18G>C Intronic	c.76G>A Gly6Ser (Likely benign)	c.424G>A Val122Ile (Pathogenic)	c.336-19G>A Intronic
Patient Count #	142	125	94	61

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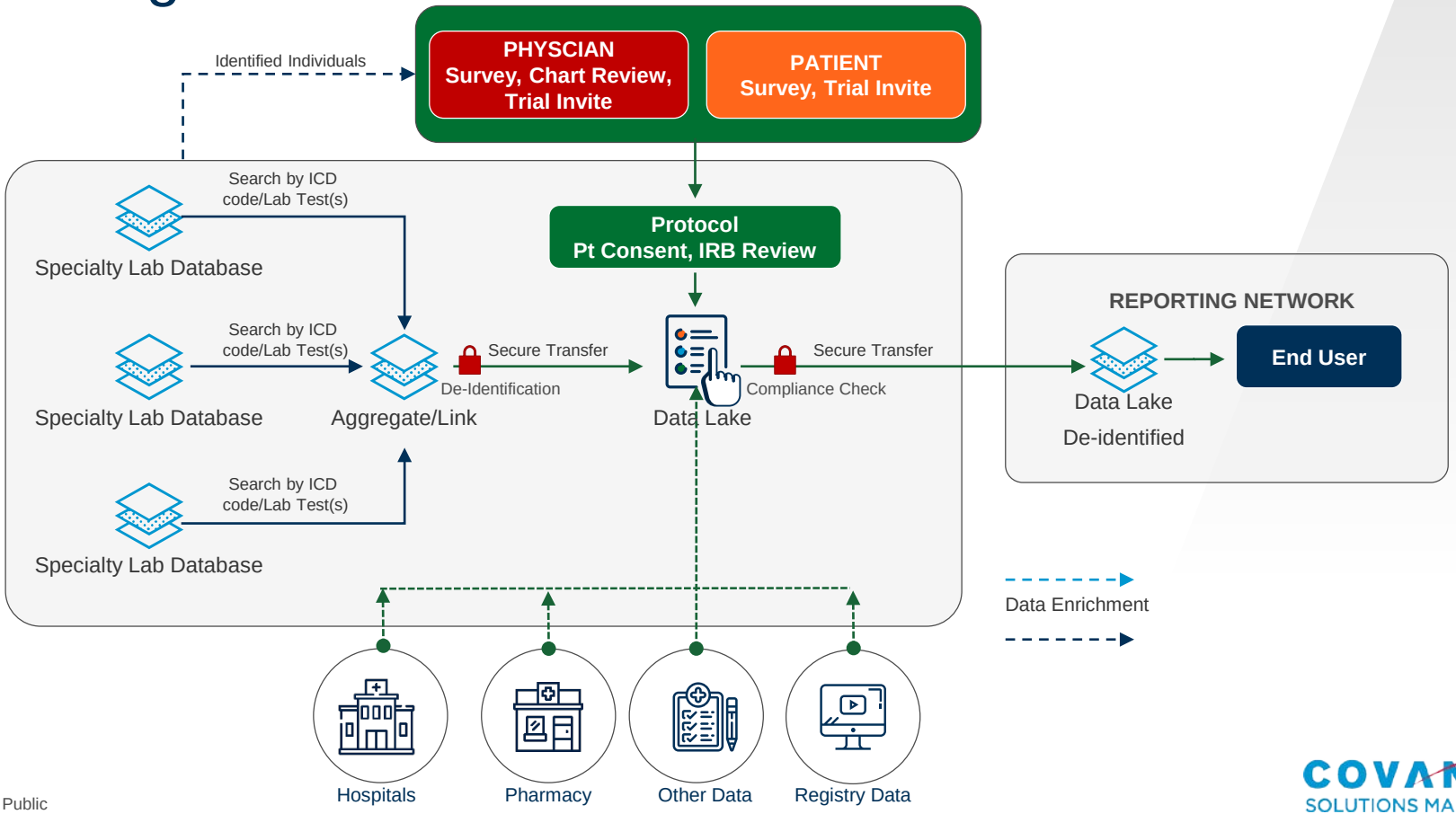
Creating a Data Lake



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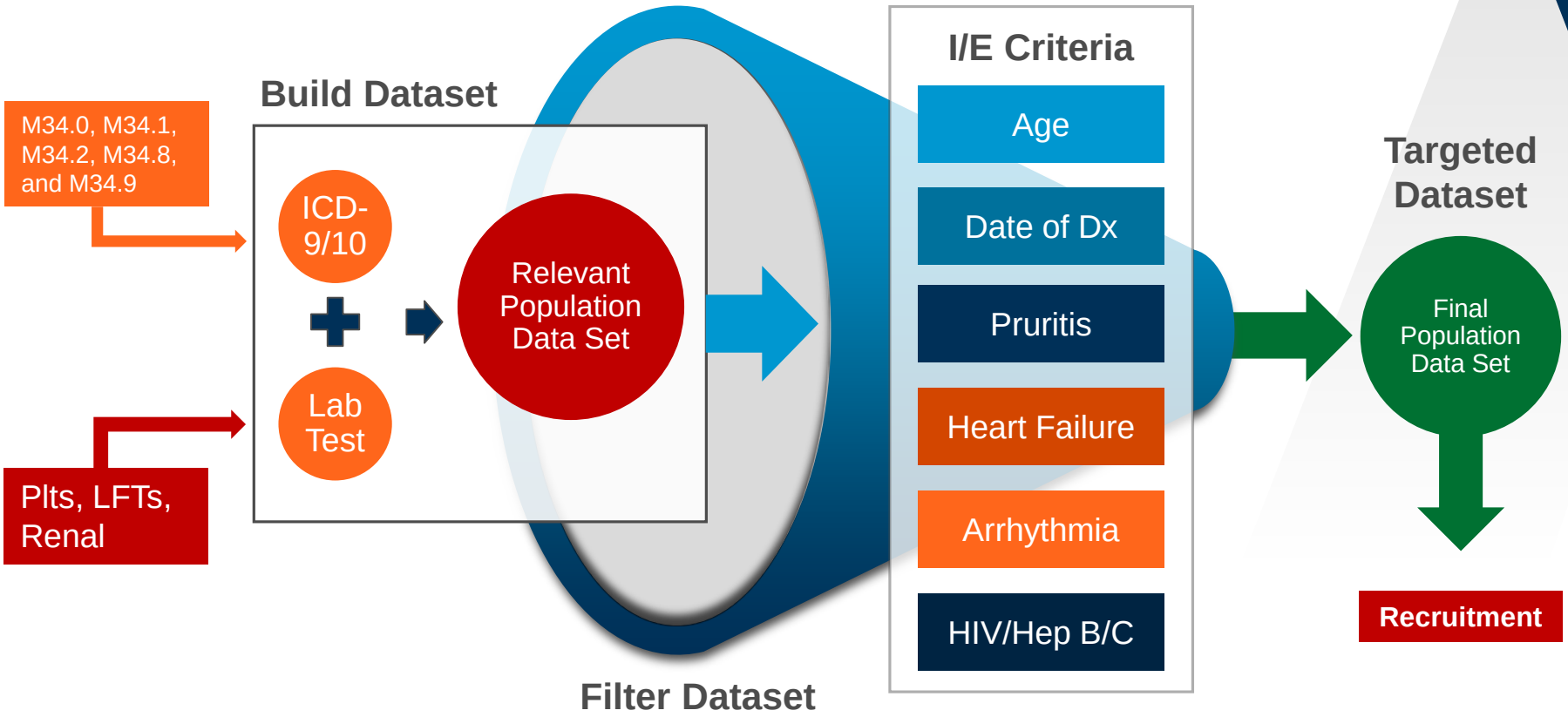
Development of a Dataset: Protocol Considerations



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Patient Care Data in Rare Diseases

PATIENTS

Delayed diagnosis

Multiple physicians

Uncertainty of disease progression

Complexity of clinical trials

Need for approved therapies

BRIDGING THE GAP

Address several key challenges for both patients and drug developers

Longitudinal objective laboratory data and physician diagnostic coding in patient care setting

Advance approaches for data analysis

Established data quality assurance procedures, understanding data limitations, exploring novel methods

Optimize protocol design and connect patients to clinical trials

DRUG DEVELOPERS

Patient identification

Identification of treating physicians

Lack of natural history data

Understanding of patient perspective

De-risk clinical development

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Leveraging Our Data Assets

Patient Data Privacy and Security

- Protecting the privacy and security of patient information is of paramount importance to LabCorp's business and key to maintaining trust of patients, study participants, and clients
- With respect to the use and disclosure of LabCorp patient data for clinical research purposes, our company is committed to compliance with all applicable federal, state, and local privacy laws, including HIPAA

Better Together Patients

- Through Better Together, patients voluntarily authorize LabCorp to disclose their lab data and demographic information to Covance for the purpose of identifying and being contacted about clinical research opportunities
- Patients provide authorization through the LabCorp | Patient™ portal or such other secure means that allow for the verification of the individual's identity
- Authorization can be revoked by the patient at any time
- Covance reviews lab data for Better Together patients, and may contact patients directly about clinical studies
- Through survey outreach, patients also provide feedback and insights on their clinical trial experiences and the burden of disease, allowing for more optimal protocol design and patient-centric approaches to study recruitment and participation

Other LabCorp Patient Data

- Outside of Better Together, LabCorp shares de-identified lab data with Covance, allowing for analysis of diseases/conditions of potential interest to study sponsors
- As a healthcare provider and HIPAA covered entity, LabCorp's use and disclosure of protected health information (PHI) is subject to HIPAA
- Any outreach by LabCorp to other healthcare providers/patients regarding clinical research that involves the use of PHI is done in accordance with the HIPAA Privacy Rule

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Frederick J. Derosier, D.O.

- D.O. from the New York College of Osteopathic Medicine; 10 years of private practice experience as an internist
- 17 years of experience, primarily in neuroscience and rare diseases, in the pharmaceutical and biotechnology industry; joined Covance in 2017
- Co-chairs the Covance pan-enterprise Advanced Therapies, Drugs, and Devices Development group which supports the development advanced therapeutic technologies,
- Executive Director, Covance Rare Diseases and Pediatrics Team, focusing on strategic considerations for patient-centric drug development within rare diseases.
- Member of the American Academy of Neurology and has authored or co-authored numerous peer-reviewed journal articles, abstracts and presentations at industry conferences
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