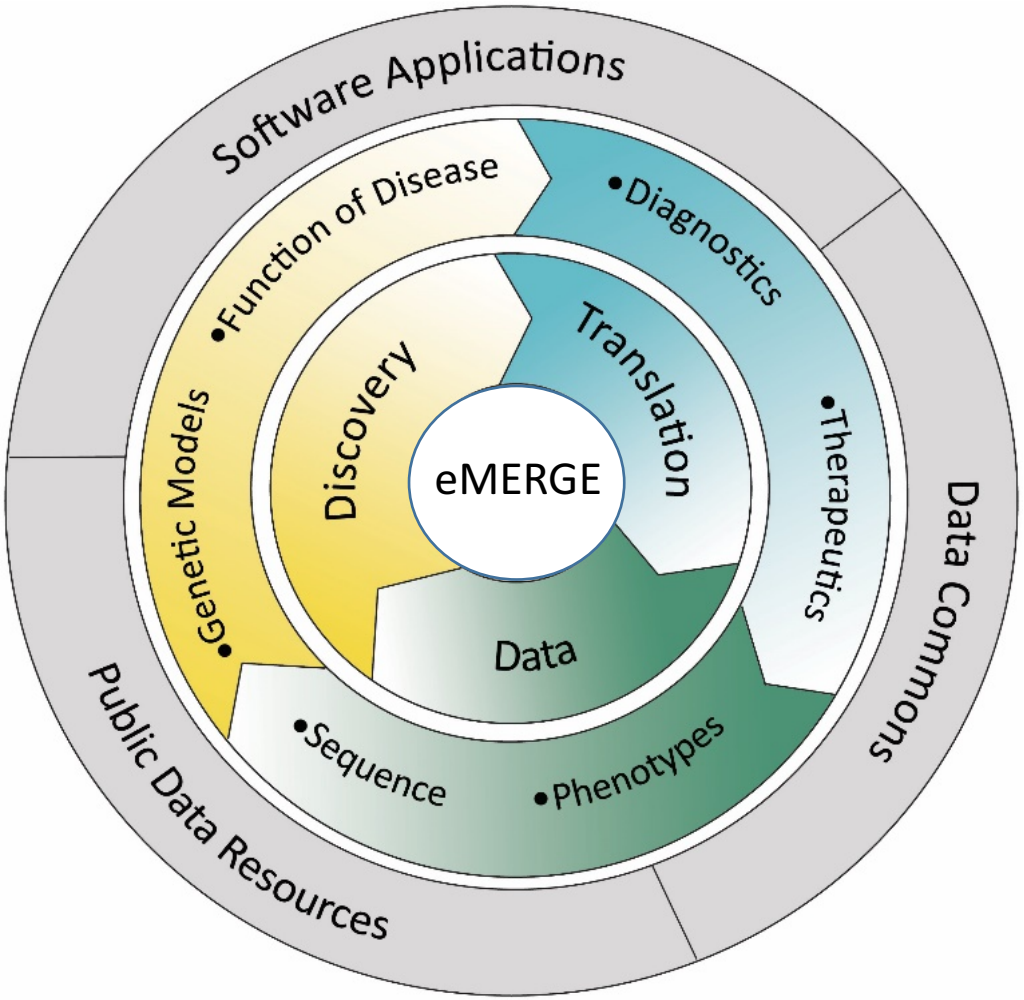
Clinical ⇔ Research Enterprises
A Virtuous Cycle



The Concept of Evidence

Experimental Discovery

"The perfect experiment"
p-values
Replication
Prior expectation

Hum Gen Discovery

p-values entrenched
1 (patent) vs a lot
(e.g. ExAC)
Replication
Prior expectation

Translation

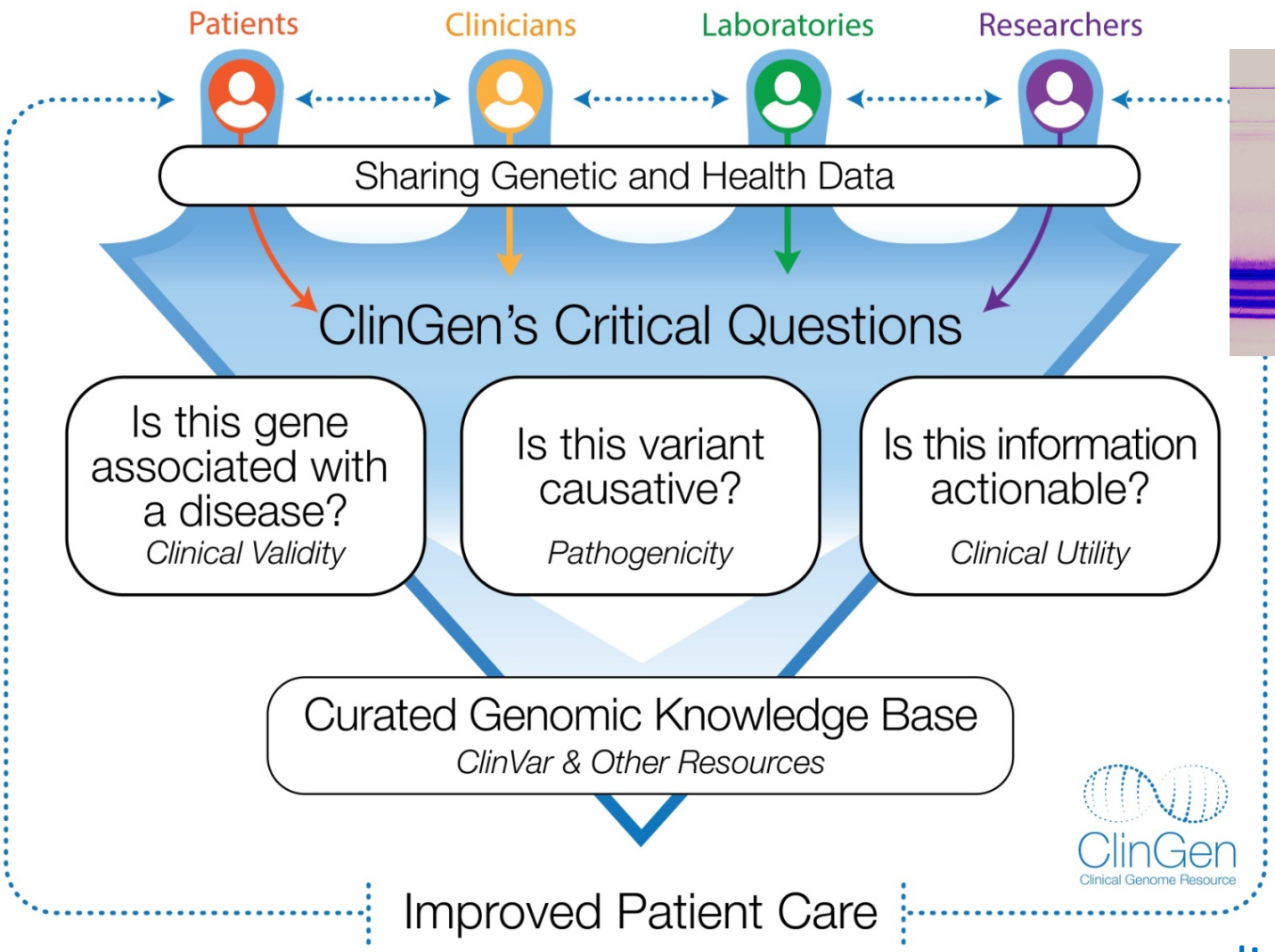
Clinical impression entrenched
Professional standards (experts and societies)
Does not like contradictory data

Evaluating the Clinical Validity of Gene-Based Associations

Strande et al. AJHG, 2017

Definitive	Role has been repeatedly demonstrated in research & clinical diagnostic settings • Upheld over time (in general, at least 3 years) • No convincing contradictory evidence
Strong	≥2 independent studies with: • Multiple pathogenic variants in unrelated probands • AND • Several different types of supporting experimental data • OR • Excess of pathogenic variants in cases vs. controls • No convincing contradictory evidence
Moderate	≥1 independent study with: • Several unrelated probands with pathogenic variants • Some supporting experimental data • No convincing contradictory evidence
Limited	≥1 independent study with: • <3 unrelated probands with pathogenic variants • OR • Multiple variants reported in unrelated probands but *without* sufficient evidence for pathogenicity • No convincing contradictory evidence
No Evidence Reported	No evidence reported for a causal role in disease (candidate genes, etc.), therefore no pathogenic variants have been identified in humans to date.
Conflicting Evidence Reported	
Disputed	Convincing evidence disputing a role for this gene in this disease has arisen • Disputing evidence need not outweigh existing evidence supporting the gene:disease association
Refuted	Evidence refuting the role of the gene in the specified disease has been reported and significantly outweighs any evidence supporting the role • Applied at the discretion of clinical domain experts after thorough review of available evidence

Clinical Genome Resource



Rehm et al. ClinGen. NEJM 2015

www.clinicalgenome.org

ClinGen Scoring System(s)

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)
Description	Case-level, family segregation, or case-control data that support the gene-disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)
Assigned Points				
CALCULATED CLASSIFICATION		**LIMITED**	**1-6**	
		MODERATE	**7-11**	
		STRONG	**12-18**	
		DEFINITIVE	**12-18 AND replication over time**	

Some comments about "actionability"

Hunter et al. (2016) Genetics in Med: Severity, Effectiveness, Nature of Intervention

What is the action?

Usually considered modified treatment or preventive measure applied to the patient.

Reporting is, by itself, an action. The patient's family? Family planning?

What is the evidence above and beyond traditional evidence (e.g. risk factors)?

e.g. Cholesterol levels vs LDLR mutation

Do we treat the genotype or the phenotype?

What is the risk/harm of a misapplied action?

It is assumed to be high, but it may be quite low in some cases

What we have seen so far is great, but……

…. it doesn’t scale.

NIH Sequencing Efforts

NIH National Heart, Lung, and Blood Institute

NIH National Human Genome Research Institute

NIH National Institute on Aging

TOPMed

- CVD Cohorts
- >130K WGS
- Multi-omics

CCDG

- LSAC Evolved
- 22K WGS Freeze
- Multiple Cohorts

emerge network
ELECTRONIC MEDICAL RECORDS AND GENOMICS

- 15K Custom Panel
- Clinical Signout
- HGSC-cl

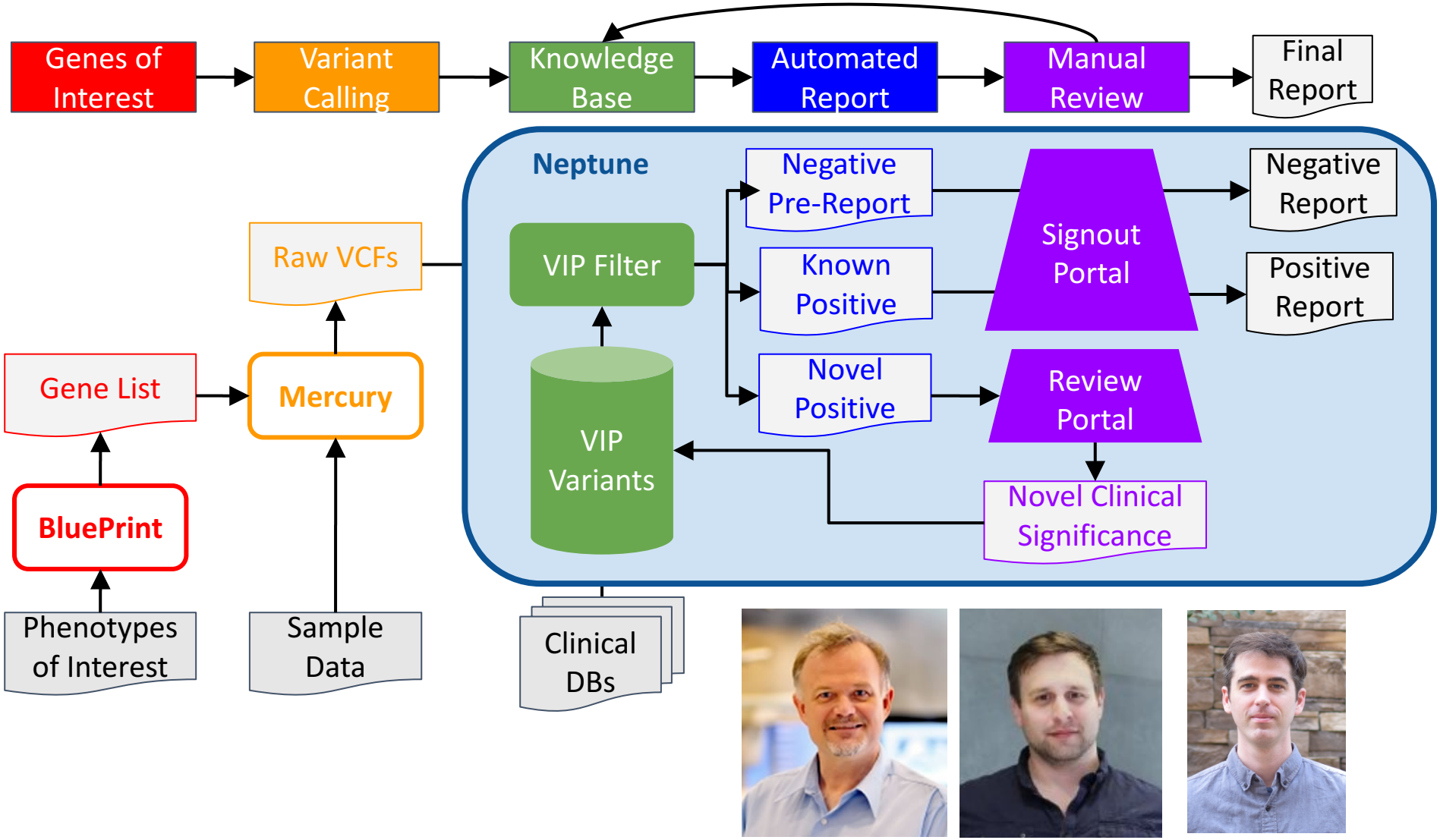
adsp
Alzheimer's Disease Sequencing Project

- 1K Family WGS
- 11K Case/Control WES

CHARGE CONSORTIUM
COHORTS FOR HEART & AGING RESEARCH IN GENOMIC EPIDEMIOLOGY

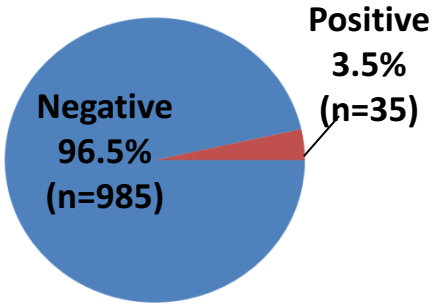
T2D-GENES

Neptune: Automated Clinical Reporting



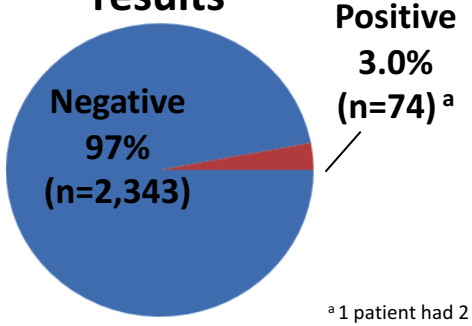
BAYLOR HGSC STATUS UPDATE: Interpretation & Reporting ALL sites, n = 2,417, Variable phenotypes

Indication based Returnable results



n = 1,020

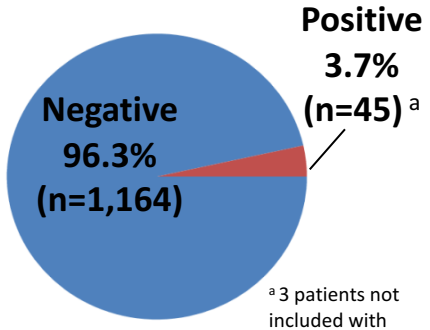
Non indication based Consensus returnable results



n = 2,417

[a] 1 patient had 2 variants

Non indication based Site-specific returnable results

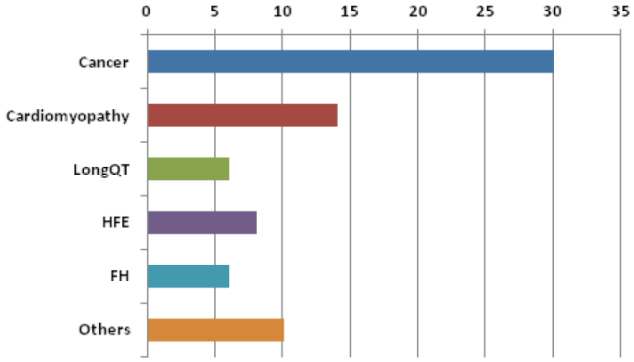


n = 1,209

[a] 3 patients not included with indication based results

Indications	Total	Pos.	Neg.
Cardiomyopathy	1	1	0
Cardiac Arrythmia	31	0	31
Hyperlipidemia [a]	637	16	621
Colorectal Cancer	279	2	277
Breast/Ovarian Cancer[b]	72	16	56

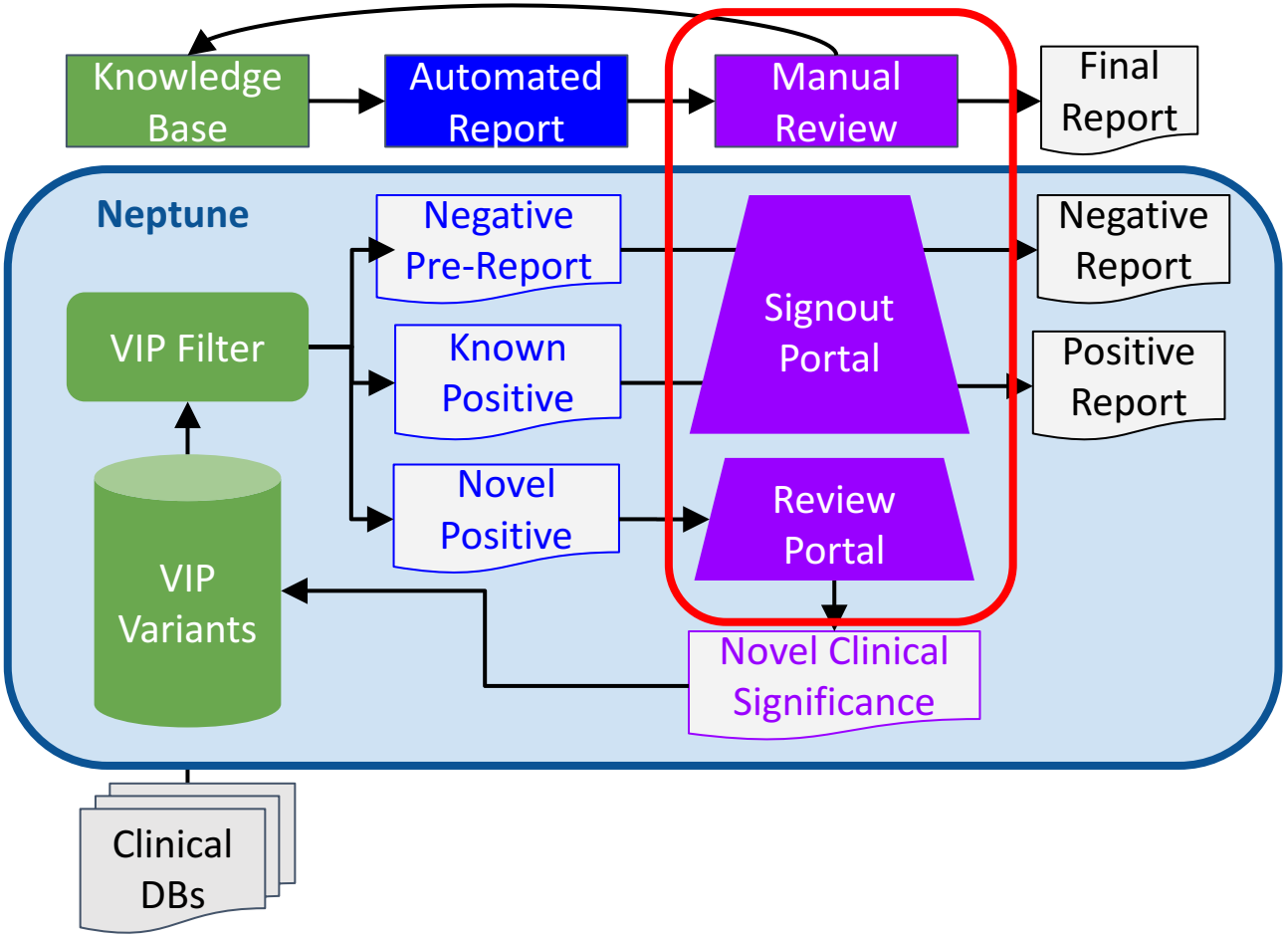
[a]Hyperlipidemia includes FH, hypertriglyceridemia, hyperlipidemia and coronary artery disease indications.
[b] All returned genes belong to the 68 consensus except for CHEK2 in a breast cancer patient



Others include MEFV, HNF1A, CACNA1A, OTC, COL3A1, SMAD3, SMAD4 (x1), MH (x3)

Path and Lpath variants in NU specific returned	Total
CHEK2	24
ATM	7
SERPINA1	2
MC4R	3
KCNE1	6
F11, FLG, KCNE2 (x1)	3

Neptune: Automated Clinical Reporting



How can expert curation be scaled?

Developing national healthcare services with crowdsourcing

Paradigm shift we've been waiting for?