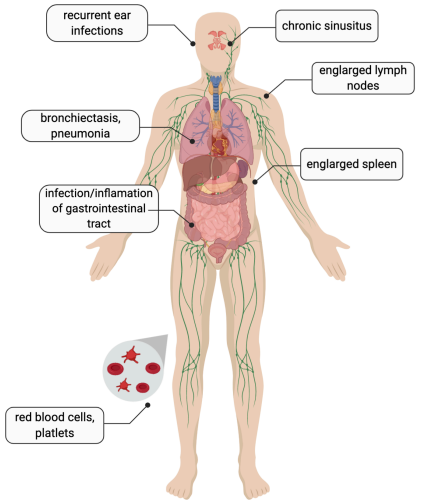
Heterogeneity of clinical manifestations leads to a significant delay in diagnosis and treatment of CVID

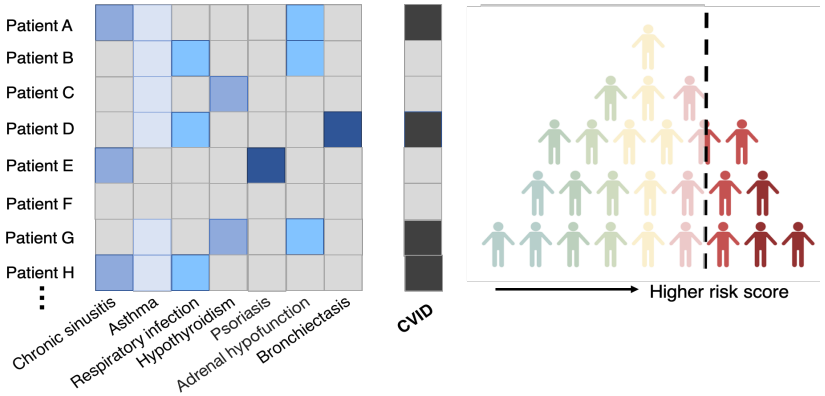
- **Common Variable Immunodeficiency Disorders (CVID)** is a heterogeneous group of disorders defined by a state of antibody deficiency
- CVID affects 1 in 25,000 to 1 in 50,000 people
- Patients get 'lost' in specialty clinics where only a subset of their symptoms are treated
- Genetic-basis is largely unknown and a single lab test cannot directly confirm diagnosis



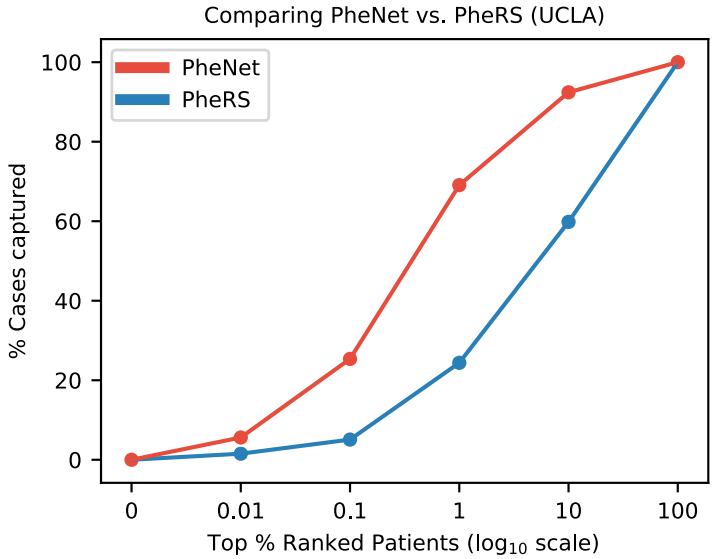
(Bonilla et al. J Allergy Clin Immunol Pract 2016; Notarangelo et al. J. Allergy Clin. Immunol. 2010)

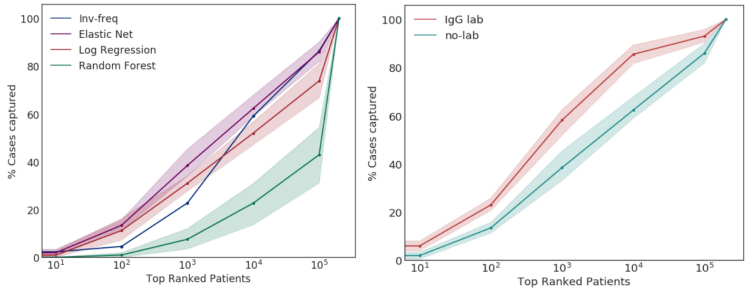
Computing a phenotype risk score from EHR

- Phenotypic patterns of CVID can be derived from both OMIM (Online Mendelian Inheritance in Man) database and current CVID patients
- Groups of billing codes and antibody laboratory tests are combined with a penalized regression framework to compute a risk score per patient



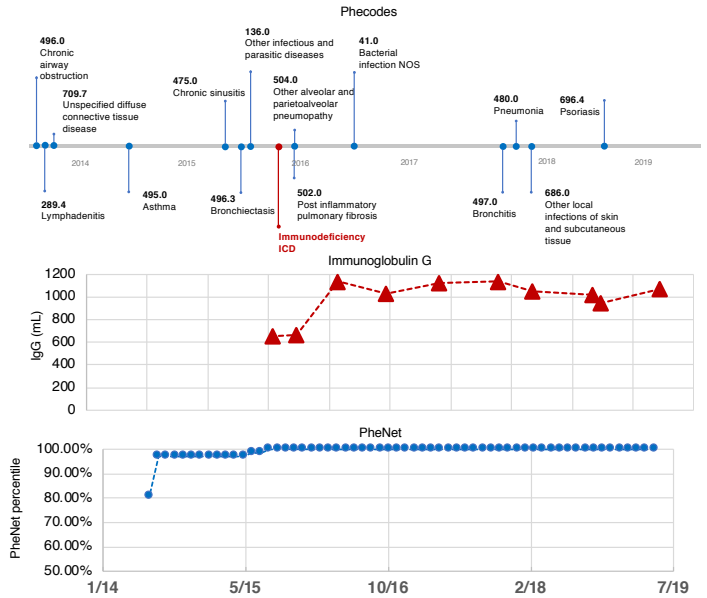
PheNet identifies 3x more patients than existing methods





- Model is trained using only 200 'ground truth' CVID patients (identified from manual review) and tested on 700K patients within the UCLA Health system
- Compared to previous models (Bastarache et al. Science 2018), PheNet shows a 3-fold improvement due to the integration of labeled data and laboratory information

PheNet identifies high-risk patients before they are formally diagnosed



Example patient that was found to be in the top percentile of the PheNet score distribution ***before*** any immunodeficiency billing code was on their medical record

Patients with top risk score have rare, pathogenic mutations

Gene	Phenotypes
ACVRL1	Epistaxis; Hereditary hemorrhagic telangiectasia type 2;Pulmonary arterial hypertension; Pulmonary arterial hypertension related to hereditary hemorrhagic telangiectasia
CDH1	Hereditary cancer-predisposing syndrome
SLCO2A1	Primary hypertrophic osteoarthropathy, autosomal recessive 2
CDH23	CDH23-Related Disorders; Deafness, autosomal recessive 12;PITUITARY ADENOMA 5, MULTIPLE TYPES; Rare genetic deafness; Usher syndrome, type 1D;Usher syndrome, type 1D;
GJB4	Erythrokeratodermia variabilis
TG	Iodotyrosyl coupling defect
CFTR	Bronchiectasis with or without elevated sweat chloride 1;Congenital bilateral absence of the vas deferens; Cystic fibrosis; Cystic fibrosis; Hereditary pancreatitis; Inborn genetic diseases; ataluren response - Efficacy;
F11	Hereditary factor XI deficiency disease
EVC2	Chondroectodermal dysplasia
LPL	Hyperapobetalipoproteinemia; Hyperlipidemia, familial combined

Out of top 1000 patients (ranked by CVID risk score), 79 patients were genotyped, and 10 patients carry a rare, pathogenic mutation