Presidential Council of Advisors on Science & Technology: Precision Medicine Initiative

The Regeneron-Geisinger Collaboration as a Model

George D. Yancopoulos, MD, PhD
President, Regeneron Laboratories
Chief Scientific Officer & Founding Scientist, Regeneron

Precision Medicine Initiative

The dream is to go from genes to a new way of promoting health

Prognosis:

Using your genome to better predict health risks, earlier and more precisely

Better diagnosis & treatment selection:

Using your genome to better discriminate between related disease states and appropriately deliver more precise treatments – the right treatments for the right patients!

Discover New Targets for Drug Development:

Using your genome find genes that cause or protect against disease, and then develop therapeutics based on these new "genetically-defined" drug targets

Human Genetics to Drugs: CAPS treatment with IL1 blockers was one of first successful examples with biologics*, PCSK9 perhaps the most highlighted

*Excludes replacement therapies for deficiency diseases (e.g. Genzyme, Biomarin, etc)

Disease/Indication	Gene/Target	Drug/Candidate
* → **Cryopyrin Associated Periodic Syndromes (CAPS)**	**CIAS1/ NLRP3**	**Arcalyst:** **IL1 Trap (Regeneron)** **Canakinumab:** **IL1 Ab (Novartis)**
* → **Hypercholesterolemia & Cardiovascular Disease**	**PCSK9**	**Alirocumab:** **PCSK9 Ab (Regeneron)** **Evolocumab:** **PCSK9 Ab (Amgen)**
Diabetes	PPARG	Thiazolidinediones, PPARɣ agonist
Pain	SCN9A (NaV1.7)	In development (Pfizer, Regeneron, Xenon, etc)
Cystic fibrosis	CFTR	Kalydeco (Vertex)
HIV/AIDS	CCR5	Selzentry/maraviroc (Pfizer)
Benign prostatic hyperplasia, male pattern baldness	SRD5A2 (5α reductase)	Finasteride (Merck)

Anti-PCKS9 Antibodies for lowering LDL-C

From Genetics to Drug: Following up the genetics, Regeneron leads therapeutics race

2003 PCSK9 GOF mutation in a single family associated with profound hypercholesterolemia (Abifadel et al. *Nat. Genet.* 34:154)

2005/6 PCSK9 LOF mutations in human populations associated with low cholesterol & decreased CV risk (J. Cohen & H. Hobbs, UTSW)

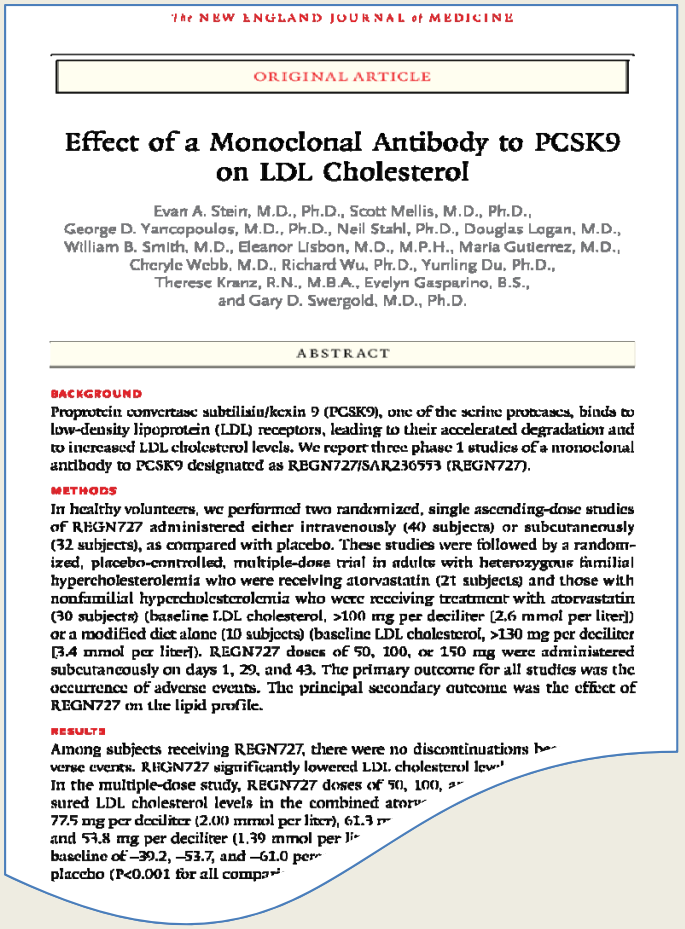
2006/7 Mouse modeling confirms causation, provides test system for Abs

2010 Regeneron first to treat human patients with PCSK9 blocking Ab

2012 Regeneron first to publish human data w PCSK9 Ab (Alirocumab) in NEJM

2013 Regeneron reports first Phase 3 data with PCSK9 Ab (ODYSSEY MONO)

2015 Regeneron has earliest potential FDA Approval, July 2015



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of a Monoclonal Antibody to PCSK9 on LDL Cholesterol

Evan A. Stein, M.D., Ph.D., Scott Mellis, M.D., Ph.D., George D. Yancopoulos, M.D., Ph.D., Neil Stahl, Ph.D., Douglas Logan, M.D., William B. Smith, M.D., Eleanor Lisbon, M.D., M.P.H., Maria Gutierrez, M.D., Cheryle Webb, M.D., Richard Wu, Ph.D., Yunling Du, Ph.D., Therese Kranz, R.N., M.B.A., Evelyn Gasparino, B.S., and Gary D. Swergold, M.D., Ph.D.

ABSTRACT

BACKGROUND

Proprotein convertase subtilisin/kexin 9 (PCSK9), one of the serine proteases, binds to low-density lipoprotein (LDL) receptors, leading to their accelerated degradation and to increased LDL cholesterol levels. We report three phase 1 studies of a monoclonal antibody to PCSK9 designated as REGN727/SAR236553 (REGN727).

METHODS

In healthy volunteers, we performed two randomized, single ascending-dose studies of REGN727 administered either intravenously (40 subjects) or subcutaneously (32 subjects), as compared with placebo. These studies were followed by a randomized, placebo-controlled, multiple-dose trial in adults with heterozygous familial hypercholesterolemia who were receiving atorvastatin (21 subjects) and those with nonfamilial hypercholesterolemia who were receiving treatment with atorvastatin (30 subjects) (baseline LDL cholesterol, >100 mg per deciliter [2.6 mmol per liter]) or a modified diet alone (10 subjects) (baseline LDL cholesterol, >130 mg per deciliter [3.4 mmol per liter]). REGN727 doses of 50, 100, or 150 mg were administered subcutaneously on days 1, 29, and 43. The primary outcome for all studies was the occurrence of adverse events. The principal secondary outcome was the effect of REGN727 on the lipid profile.

RESULTS

Among subjects receiving REGN727, there were no discontinuations be-
verse events. REGN727 significantly lowered LDL cholesterol lev-
In the multiple-dose study, REGN727 doses of 50, 100, a-
sured LDL cholesterol levels in the combined atorv-
77.5 mg per deciliter (2.00 mmol per liter), 61.3 m-
and 53.8 mg per deciliter (1.39 mmol per li-
baseline of −39.2, −53.7, and −61.0 per-
placebo (P<0.001 for all compar-

Regeneron-Geisinger Foundational Collaboration to Sequence >250,000 People in the Geisinger Health System

The New York Times

Aiming to Push Genomics Forward in New Study

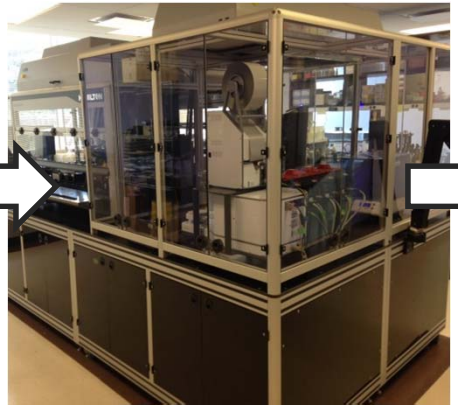
By ANDREW POLLACK JAN. 13, 2014

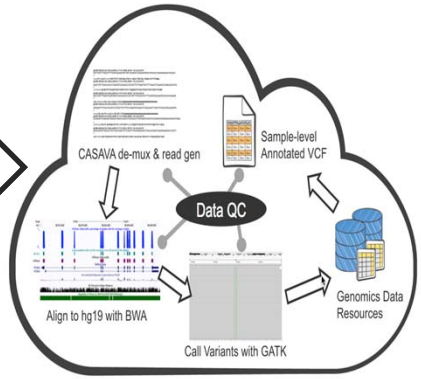
"Scientifically and medically, it's pretty exciting," said Dr. Leslie G. Biesecker, chief of the genetic disease research branch at the government's National Human Genome Research Institute, who is familiar with the project. "As far as I'm aware, it's the ***largest clinical sequencing undertaking in this country so far by a long shot."*** *He added that the move of sequencing into general health care* ***"is going to change medicine."***

- First major collaboration of its kind between a leading biotechnology company and a leading health care provider/payer
- Geisinger: >2.5 million patient health system with "cradle to grave" records; amongst earliest adopters of EHRs, and leaders in clinical informatics
- Goals:
  - First, build the world's most comprehensive genotype-phenotype resource combining de-identified genomic and clinical data from >250,000 people to aid drug development and genomic medicine
  - Then, turn the genomic data into medically actionable information by translating genetic discoveries into improved patient outcomes and therapeutics

Regeneron's Innovative Technologies & Automation Enable Ultra High-Throughput Sequencing & Analysis

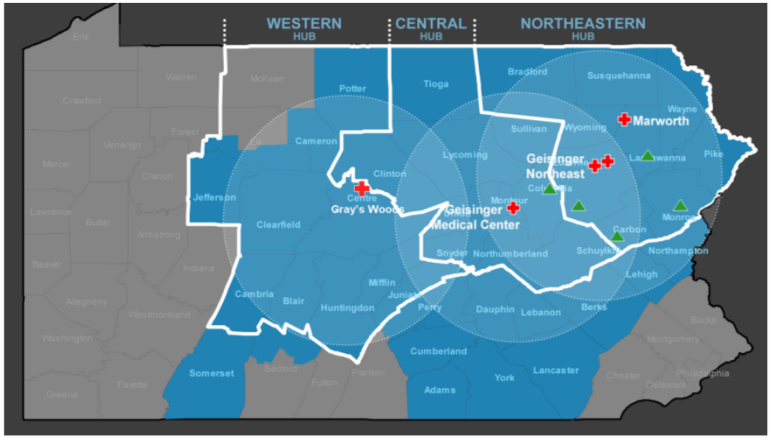
Automated Biobank (1.4M Samples)	Library Prep Automation (>200,000 Samples/Yr)	Illumina Fleet (>80,000 Exomes/Yr)	Cloud Based Informatics & Analysis





- **Key Technologies and Capabilities**
  - Automated biobank with 1.4M+ sample capacities
  - Custom fully-automated exome and targeted sequencing sample preparation workflows
  - Exome sequencing capabilities of >80,000 individuals per year and targeted sequencing projects (several hundred gene panel) of >100,000 individuals completed in a few months
  - First genome center "in the cloud" with fully automated analysis pipelines

Large Population-Based Study with Geisinger: Integrating Genetics and Longitudinal Health Records



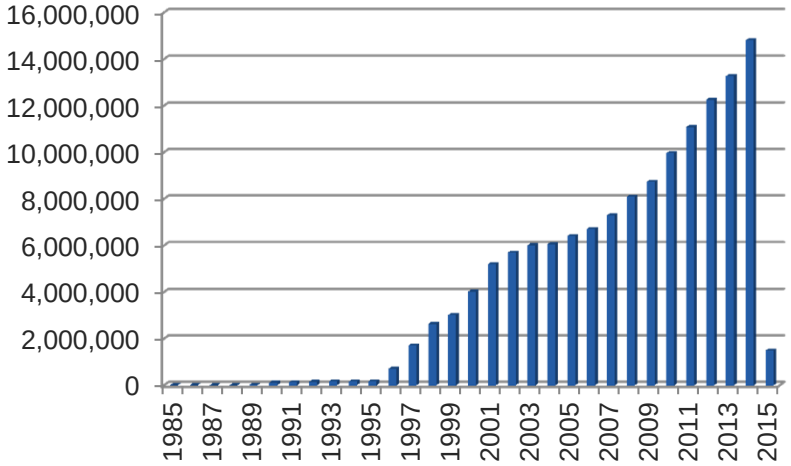
- Greater than 2.5 million people in Geisinger's catchment area
- ~18 outpatient visits and 7 years of longitudinal records per patient on average and >1.6M outpatient visits at Geisinger per year

Engaging Geisinger community as Volunteers & Participants in this effort:

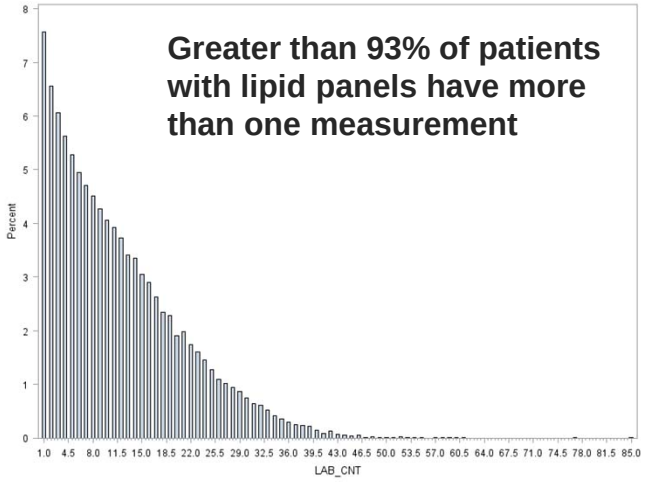
- >80,000 consented to date (>90% consent rate, broad consent for research & data sharing) → already >50,000 samples collected for genomic analysis → **40,000 already sequenced**
- Breakdown of consented population includes large unselected populations as well as targeted efforts in diseases of interest and deeply phenotyped patients
  - Cardiac catheterization lab (~8,000)
  - Bariatric surgery (~4,000) → one of the largest in the world
- ***Key differentiator:*** *Geisinger is the world's largest longitudinal "live" population in which iterative call back phenotyping and sample collection are operationalized*

In-Depth, Longitudinal Health Records Provide a Rich Resource for Genetic Discoveries

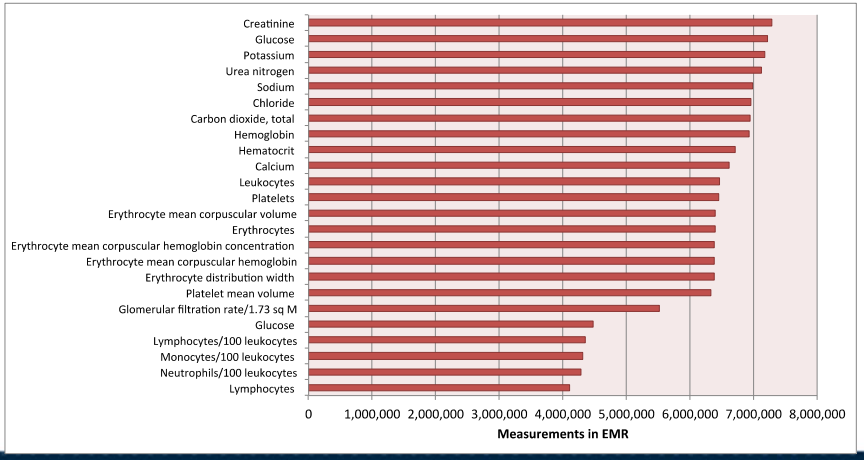
GHS Clinical Encounters by Year



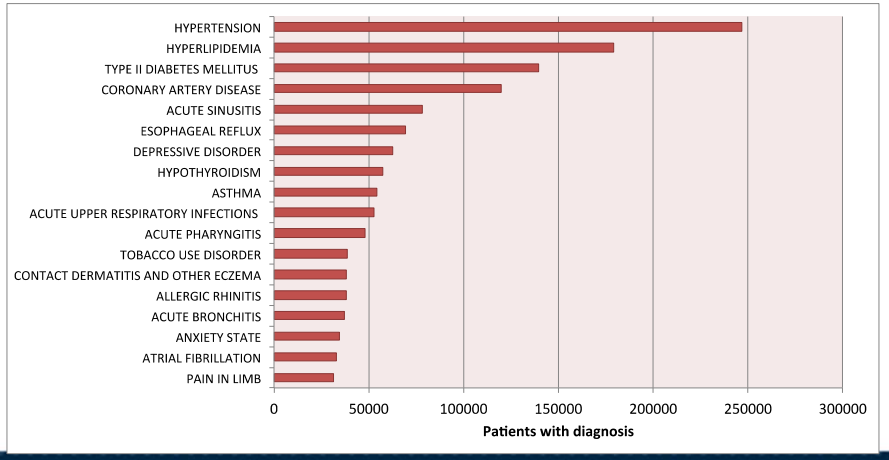
Repeat Fasting Lipid Panels in GHS EHR



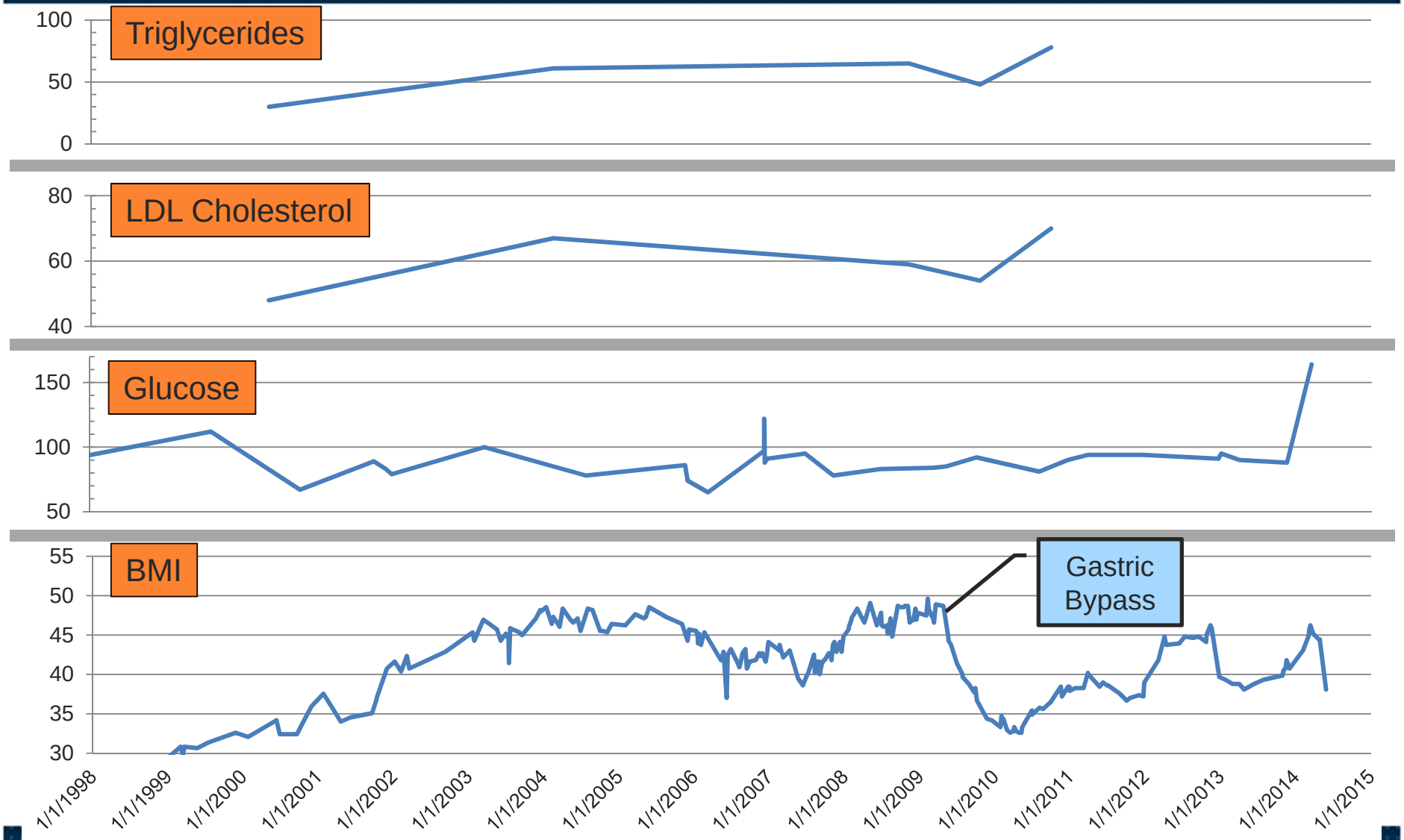
Most Prevalent Labs in GHS EHR



Most Prevalent Office Visit Dx in GHS EHR



In Depth Review of De-identified Longitudinal Health Records



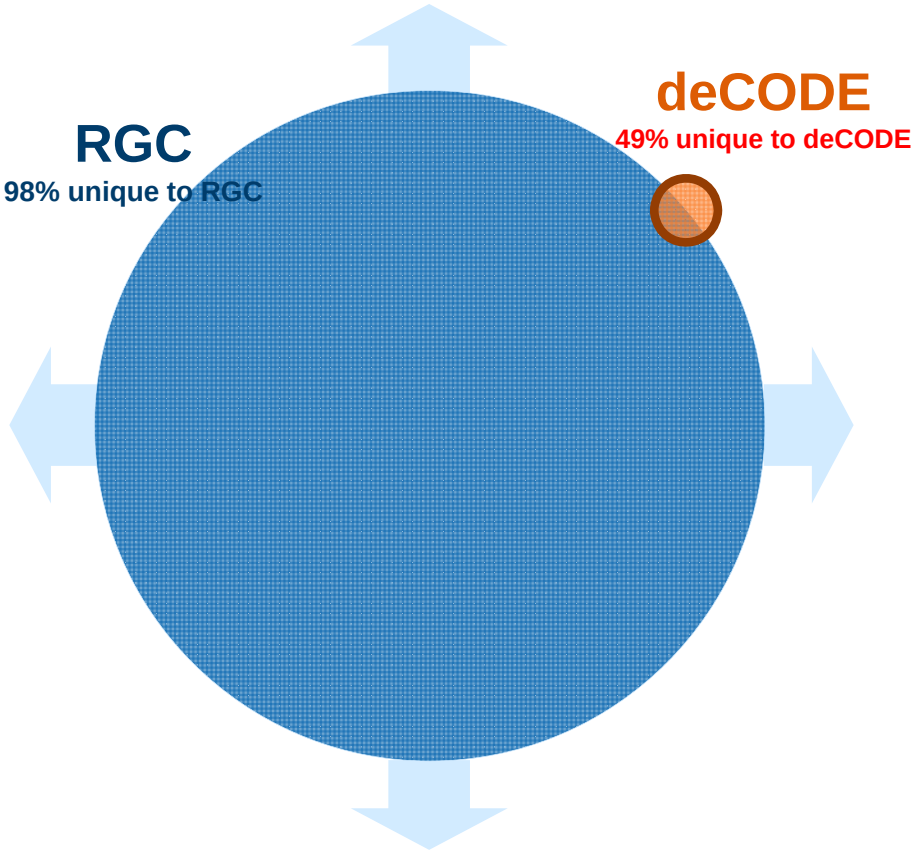
deCODE Genetics has pioneered the field in this area

LOF's of great interest (Human "Knockouts"): comparing deCODE's LOFs to those in interim analysis of the first 31,000 individuals from Regeneron-Geisinger Collaboration (RGC)

- RGC has identified >25x more predicted LOF variants (in first 31,000 individuals) than deCODE reported (from 2,636 Icelanders)
  - **RGC has identified ~51% of unique LOFs observed by deCODE**
  - **deCODE has identified only 2% of unique LOFs that were observed by RGC**
- In first 31,000 individuals, RGC finds ~90% of genes are affected by at least one LOF
  - deCODE finds only ~26% of genes affected
- RGC finds at least one homozygous LOF carrier for 2,610 gene,s vs 1,171 for deCODE
- Signal to noise
  - RGC: 188,614 unique LOFs out of ~6.1M exonic variants from WES of 31,508 individuals
  - deCODE: 7,399 unique LOFs and ~470K exonic variants out of ~20M WGS variants in 2,636 people

RGC-GHS Have Identified ~25x More LOFs Than Recently Reported by deCODE Genetics

Number of Unique LOF Variants (drawn to scale)

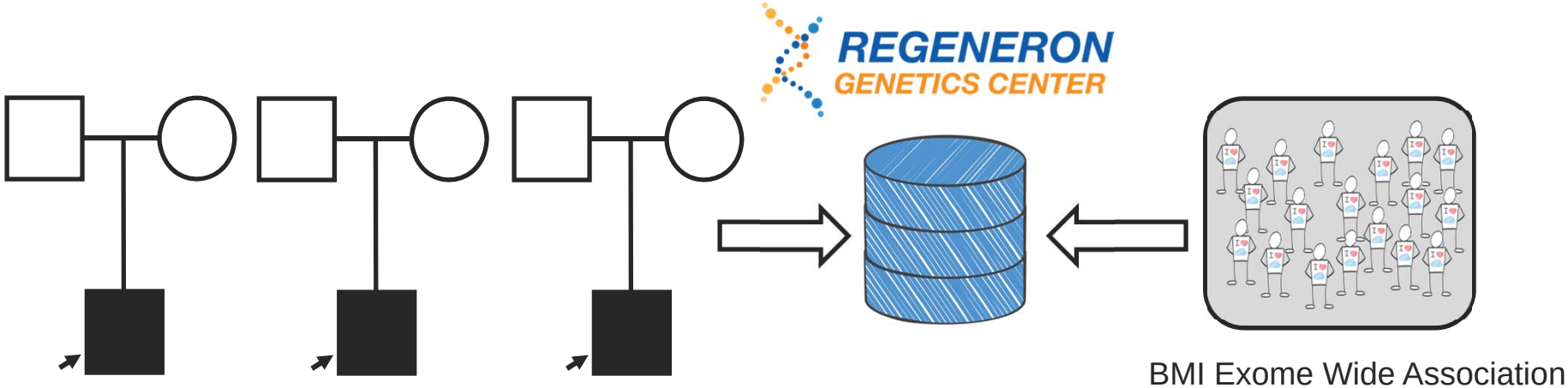


		RGC	deCODE
# unique LOFs in exome	Total	188,614	7,399
	RGC only	184,829	-
	deCODE only	-	3,614
	RGC & deCODE	3,785	
Potential		Growing	Saturated

RGC Interim analysis of >31,000 Individuals Nominates Multiple New Lipid Genes and Functional Variants

Trait	Single marker at $P < 5x10^{-8}$	LOF only at $P < 1x10^{-7}$	LOF+rare NS at $P < 1x10^{-7}$	LOF+strict deleterious NS at $P < 1x10^{-7}$	LOF+rare deleterious NS at $P < 1x10^{-7}$
HDL-c	*CETP, APOC3, APOC2, LPL, CD300LG, APOA4, LIPG, LIPC, ANGPTL4, BUD13, APOB, HNF4A, FADS1/FADS2, APOC2, ABCA1, LCAT, 8 novel*	*APOC3, ABCA1*	*APOC3, 3 novel*	*APOC3, 2 novel*	*APOC3, CETP, 4 novel*
LDL-c	*BCAM/TOMM40/APOE, PCSK9, LDLR, APOB, SORT1/CELSR2, FADS1/FADS2, 4 novel*	*2 novel*	*LDLR*	*LDLR, APOE*	*LDLR*
Triglycerides	*GCKR, APOA5/APOA4/APOC3, LPL, FADS1, MLXILPL, ANGPTL3/DOCK7, CD300LG, APOB, ANGPTL4, TM6SF2, 5 novel*	*APOC3*	*APOC3*	*APOC3, APOE*	*APOC3*

Families to Populations at the RGC: An Illustrative Example in Severe Obesity



Severe Obesity Families

BMI Exome Wide Association Study in Geisinger

Findings from Family Studies

- Many novel candidate Mendelian disease genes identified through family studies in severe, early-onset obesity

Expanded in Population Studies

- Genes identified through family studies are queried across the Geisinger population to further our understanding and establish associations with BMI/obesity in the general population
- Example: Carriers of loss-of-function variants in a novel candidate gene, first identified through family studies in severe obesity, have higher BMI (~3 BMI units, 15-20lbs) in the GHS population

Precision Medicine Initiative

The dream is to go from genes to a new way of promoting health

Prognosis:

Using your genome to better predict health risks, earlier and more precisely

Better diagnosis & treatment selection:

Using your genome to better discriminate between related disease states and appropriately deliver more precise treatments – the right treatments for the right patients!

Discover New Targets for Drug Development:

Using your genome find genes that cause or protect against disease, and then develop therapeutics based on these new "genetically-defined" drug targets