From Gene Discoveries to Therapeutic Opportunities: Genetics Guided Drug Discovery & Development at Regeneron

Deriving Drug Discovery Value from Large-Scale Genetic Bioresources: March 22, 2016 IOM Workshop Meeting

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The Need for Human Genomics in Drug Discovery; Enormous Potential for the Current Era of Genomic Discovery

- 95% of experimental medicines fail, with costs exceeding $5B per approved drug
- Decades of innovations spanning small molecules to biologics have addressed many bottlenecks in the drug development process
- One of the biggest current bottlenecks is well validated targets: ~500-1,000 genes (<5% of all genes) account for all targets of approved and experimental medicines
- Human genetics is a validated approach to target identification and drug development
  - Successes: cancer genomics and targeted therapies, rare diseases, NHGRI/NCI sequencing centers and programs, deCODE genetics, and many many more
  - **Improved probability of success for drugs with supporting human genetics**
- Technology and cost revolutions enabling genomics initiatives of unprecedented scale that will unlock important new discoveries and medicines
- **You cannot pursue modern drug discovery & development without incorporating human genetics into your R&D approaches**

Human Genetics in Drug Discovery: "Experiments of Nature" Guide the Way to Therapeutic Targets – Selected Examples

Gene/Target	Drug/Candidate	Disease/Indication	Genetic Model & Phenotypes
NLRP3	Arcalyst® (rilonacept), ILARIS® (canakinumab), IL-1 blockers	Cryopyrin Associated Periodic Syndromes	GOF mutations → overproduction of IL-1 → IL-1 associated autoimmune disorders
PCSK9	Praluent® (alirocumab), Repatha™ (evolocumab), bococizumab	Familial hypercholesterolemia, primary/ secondary prevention of ASCVD	Autosomal dominant (GOF) Familial Hypercholesterolemia LOF mutations → low LDL-C, decreased CVD
SCN9A	In development (Pfizer, Regeneron, Xenon, etc)	Pain	GOF mutations → paroxysmal extreme pain disorder LOF mutations → congenital insensitivity to pain (CIP)
CCR5	Selzentry® (maraviroc), CCR5 antagonist	HIV/AIDS	Naturally occurring genetic variation protects against HIV infection
PPARG	Thiazolidinediones, PPARɣ agonists	Diabetes	LOF mutations → familial severe obesity and insulin resistance
APOC3	Volanesorsen (IONIS-APOCIII$_{Rx}$), APOC3 antisense	Familial Chylomicronemia Syndrome, Familial Partial Lipodystrophy	LOF mutations → reduced TG, higher HDL, reduced CHD risk
SRD5A2	Proscar/Propecia (finasteride)	Benign prostatic hyperplasia, male pattern baldness	Rare recessive disorder → pseudohermaphroditism, ambiguous genitalia, small prostate
P2RY12	Plavix® (clopidogrel), Brilinta® (ticagrelor), Effient® (prasugrel), P2Y12 inhibitors	Antiplatelet agent (CVD prevention)	LOF mutations → congenital bleeding
SLC5A2	Jardiance® (empagliflozin), Farxiga® (Dapagliflozin), gliflozins/SGLT2 inhibitors	Diabetes	LOF mutations → familial renal glucosuria in absence of hyperglycemia
CFTR	Kalydeco® (ivacaftor)	Cystic fibrosis	Deficient CFTR channel → cystic fibrosis

Regeneron's Goals for Human Genetics

The RGC applies large-scale, fully-integrated human genetics to advance science, guide the development of therapeutics, and improve patient outcomes.

INDICATION DISCOVERY

Identify new indications for drug targets and programs

TARGET DISCOVERY

Identify new drug targets and pathways

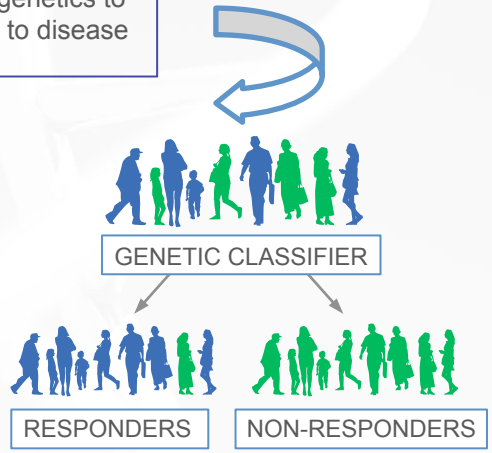
HUMAN GENETICS

VELOCIGENE

MOUSE GENETICS

BIOMARKERS

Utilize pharmacogenetics to predict response to disease

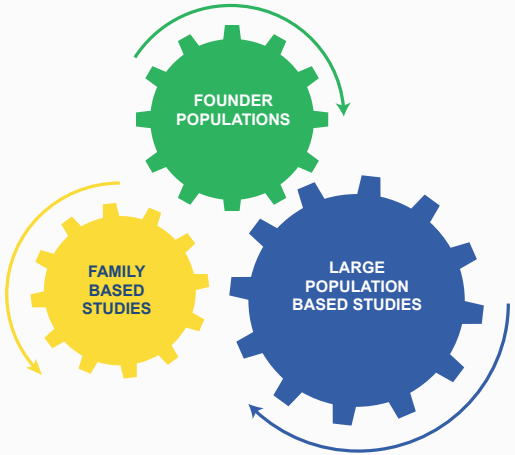


Genetics-guided Drug Development

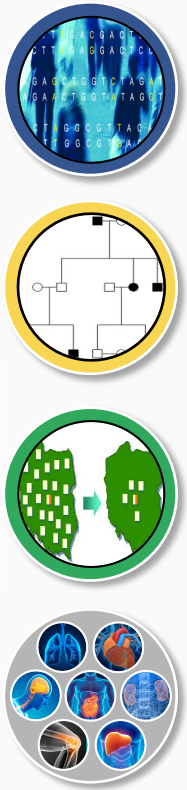
- ✓ Human genetics delivers hypotheses for targets, indications, and biomarkers
- ✓ Biological validation through *VelociGene* and deep biology
- ✓ Genetics-guided drug development improves efficiency, timelines, and probability of success

Breadth of Human Genetics Resources Across Genetic Trait Architectures and Phenotypes: RGC Network of 20+ Collaborators

Integrated approaches across genetic trait architectures . . .



. . . will fuel genomic discovery



General Population

Geisinger · LABioMed · Lund University

Family Based Studies

Columbia University Medical Center · SickKids · BCM Baylor College of Medicine · NIH National Institutes of Health

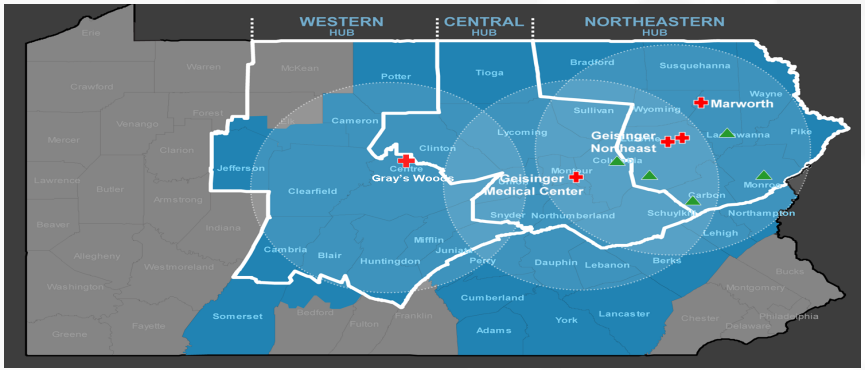
Founder Populations

ECOGENE-21 · University of Maryland Medical Center · Clinic For Special Children TREATING THE WHOLE CHILD

Phenotype Specific Cohorts

Duke University · UT Southwestern Medical Center · University of Utah Health Care · UConn Health Center · Penn Medicine

DiscovEHR Study: A Large Population-based Study to Sequence >250,000 Participants, Integrating Genetics and Longitudinal EHRs

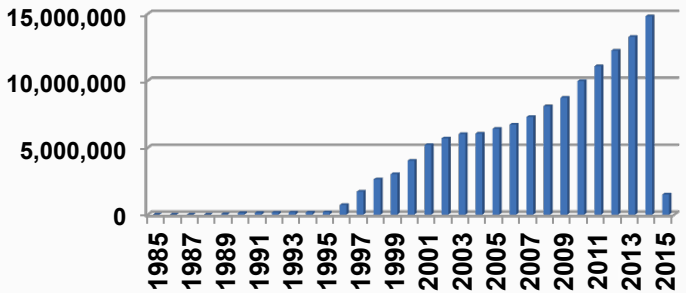


- **Geisinger and Regeneron:** two organizations focused on translating genetic discoveries into improved patient outcomes and therapeutics
- >2.5 million patient health system with “cradle to grave” records and decades of longitudinal EHRs
- >100,000 patients consented → **>60,000 sequenced and genotyped** (and counting)
- Large unselected population as well as targeted recruitment
  - Cardiac catheterization lab
  - Bariatric surgery

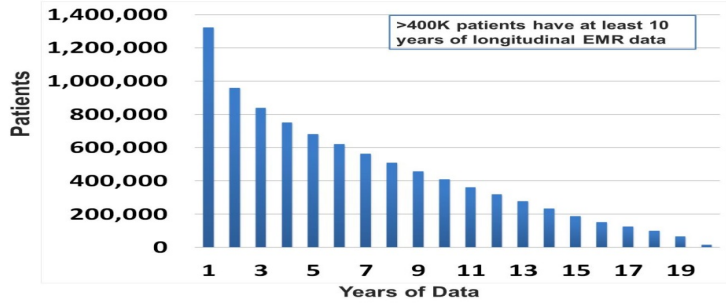
Key differentiator: *Geisinger is the world’s largest longitudinal “live” population in which iterative call back phenotyping and sample collection are operationalized*

High Density, Longitudinal Health Records Provide a Rich Resource for Genetic Discoveries

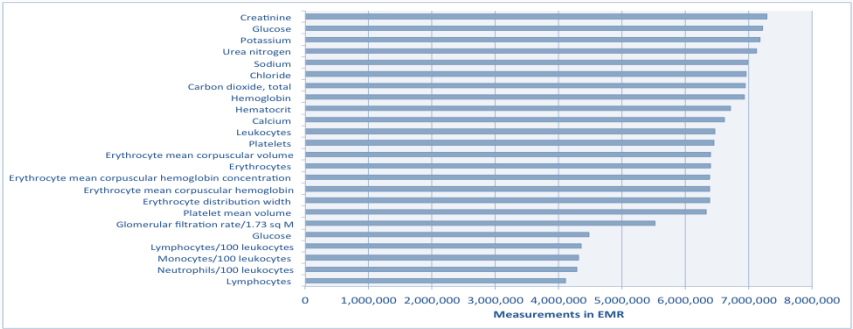
GHS Clinical Encounters by Year



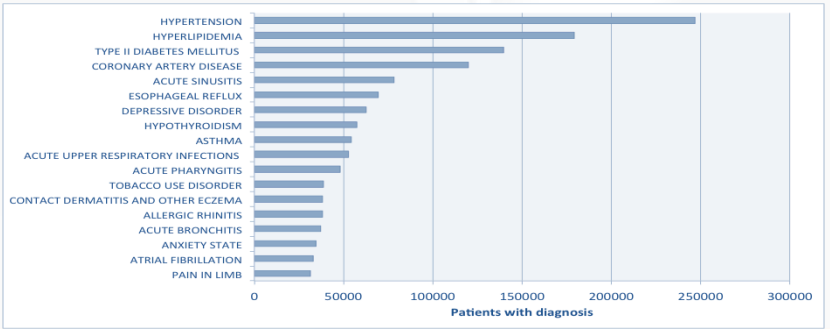
Patients by Years of Clinical Data



Most Prevalent Labs in GHS EHR

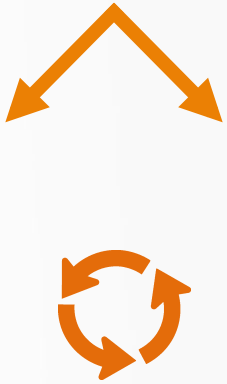


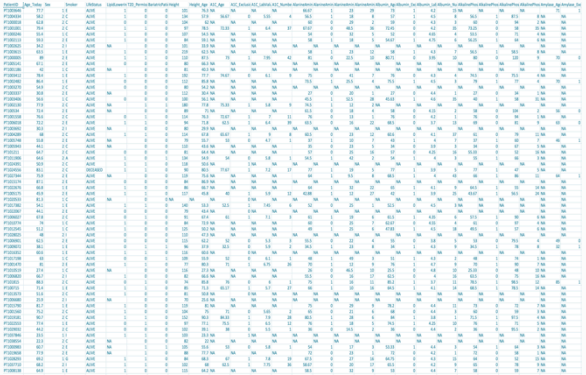
Most Prevalent Office Visit Dx in GHS EHR

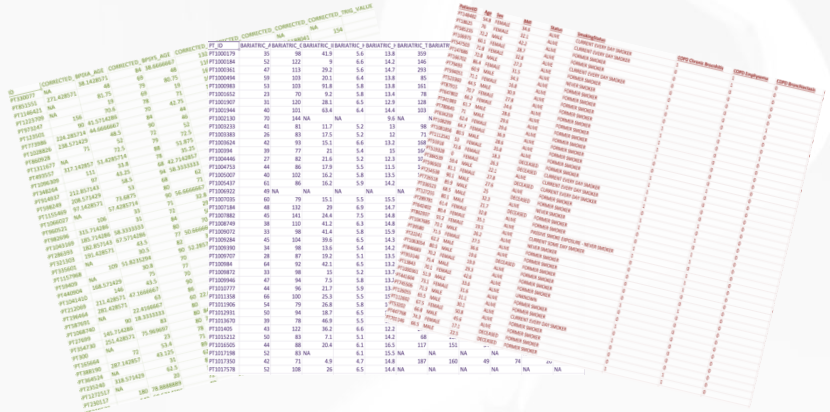


The RGC and GHS Have Developed A Large Number of High-quality, EMR-derived Phenotypes For Genetic Analyses

- A constantly growing library of more than 2000 quantitative and qualitative traits are available for high-throughput and in-depth genotype-first and phenotype-first analyses:







Binary and Quantitative Trait Matrices:

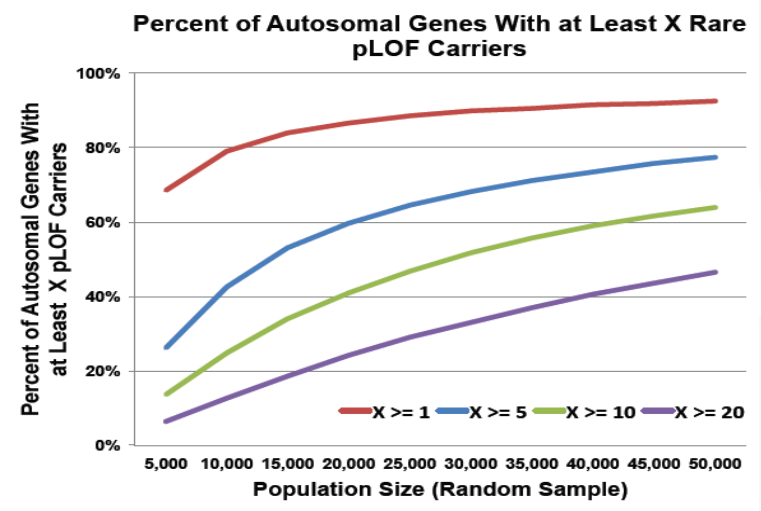
Include PheWAS, Immune, Lab Traits, DEXA, Echo, EKG, Ocular Measures, PFT's, Vitals and Anthropometrics

Deep Dive Datasets:

Examples include Coronary Artery Disease and Lipids, COPD and Asthma, Bariatric Traits and Liver Histology, Gout

Functional Variant Discovery Requires Sequencing At Scale: A Large Collection of Predicted LOF Variants in the Geisinger Database

Percent of Autosomal genes (n = 18,316) with LOF carriers (MAF < 1%)		
	Number of autosomal genes	Percent of autosomal genes
Heterozygous individuals		
>=1	17,409	92%
>=5	14,598	77%
>=10	12,093	64%
>=20	8,803	47%
Homozygous individuals		
>=1	1,313	7%
>=5	312	2%
>=10	161	1%
>=20	81	0.4%



- DiscovEHR study: 50,726 participants to date with exome sequence and longitudinal EHR
- >92% of genes with one or more heterozygous loss of function (LOF) carriers
- >1,300 (~7%) genes with homozygous LOFs, including many Regeneron drug targets

Novel Association Discovery: Inactivating Mutations in ANGPTL3 and ANGPTL4 and Reductions in CAD Risk

Table 2. Association between *ANGPTL4* E40K or Other Inactivating Mutations and Lipid Levels.*

Lipid	Noncarriers (N=41,177)	E40K Heterozygotes (N=1661)	E40K Homozygotes (N=17)	P Value†	Heterozygotes with Other Inactivating Mutation (N=75)	P Value‡
		median (IQR)			*median (IQR)*	
Triglycerides — mg/dl	132 (95–182)	115 (85–157)	81 (61–122)	2.0×10^{-23}	115 (78–162)	0.02
HDL cholesterol — mg/dl	48 (40–59)	52 (43–63)	67 (54–72)	1.6×10^{-17}	54 (44–62)	0.009
LDL cholesterol — mg/dl	114 (94–135)	116 (96–138)	107 (89–132)	0.20	119 (101–136)	0.60
Total cholesterol — mg/dl	195 (172–218)	196 (173–219)	182 (168–209)	0.90	193 (179–208)	0.80

Table 3. Association between *ANGPTL4* E40K or Other Inactivating Mutations and Coronary Artery Disease.*

Variants	Allele Frequency		Odds Ratio (95% CI)	P Value
	CAD Cases	CAD Controls		
E40K mutation in 1661 heterozygotes and 17 homozygotes	1.71	2.10	0.81 (0.70–0.92)	0.002
Heterozygous inactivating mutations in 75 participants	0.06	0.10	0.56 (0.32–1.00)	0.05

Dewey et al, Inactivating Variants in ANGPTL4 and Risk of Coronary Artery Disease, NEJM, 2016.

Background

- Regeneron's evinacumab (ANGPTL3 antibody) is in late stage development for dyslipidemias (FDA orphan designation for homozygous FH)
- ANGPTL3 and ANGPTL4 are related endogenous inhibitors of lipoprotein lipase

RGC/GHS Findings

- Low frequency coding variant in ANGPTL4 (E40K variant) ➔ reduced odds of CAD and T2D
- LOF variants in ANGPTL4 associated with larger reductions in risk of T2D and CAD
- Ongoing analyses of ANGPTL3 LOF variants suggest marked reductions in CAD risk

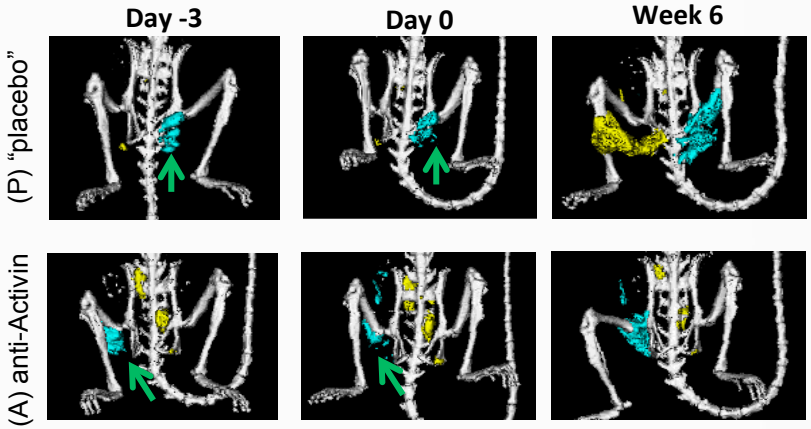
Gene Discovery in Familial Pulmonary Arterial Hypertension: TBX4 Implicated in Multiple PAH Families

Columbia University Medical Center

GENE	GENE NAME	# VARIANTS	# FAMILIES/PROBANDS	% COHORT	PAH-ASSOCIATED OMIM DISEASE
BMPR2	bone morphogenetic protein receptor, type II	20	6 families; 14 singletons	13.4%	Familial Primary Pulmonary Hypertension 1 (PPH1), with or without HHT [MIM #178600]
ACVRL1	activin A receptor type II-like 1	4	1 family; 3 singletons	2.6%	Hereditary Hemorrhagic Telangiectasia type 2 (HHT2) [MIM #600376]
KCNK3	potassium channel, two pore domain subfamily K, member 3	3	1 family; 2 singletons	2.0%	Primary Pulmonary Hypertension-4 (PPH4) [MIM #615344]
CAV1	caveolin 1, caveolae protein, 22kDa	1	1 singleton	0.6%	Primary Pulmonary Hypertension-3 (PPH3) [MIM #615343]
ENG	endoglin	2	2 families	1.3%	Hereditary Hemorrhagic Telangiectasia type 1 (HHT1) [MIM #187300]
SMAD9	SMAD family member 9	3	1 family; 2 singletons	2.0%	Primary Pulmonary Hypertension-2 (PPH2) [MIM #615342]
TBX4	**T-box 4**	**16**	**10 families; 6 singletons**	**10.7%**	**NA**

- **~71 families and 192 singletons recruited through CUMC; enriched for pediatric onset PAH**
- **Rare, deleterious variants in TBX4 identified in 16 different cases (10 families & 6 singletons)**

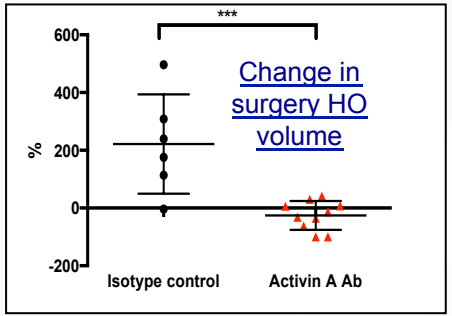
Translating Genetics to Therapeutics: Inhibition of Activin A as a Potential Therapeutic Approach in FOP



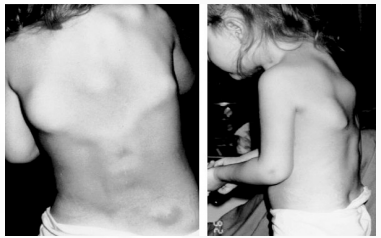
- Fibrodysplasia Ossificans Progressiva (FOP) is a rare (1 in 2,000,000) disorder that results in cumulative heterotopic ossification (HO) leading to severe disability and early mortality
- FOP results from mutations in the intracellular domain of ACVR1 (ALK2), a BMP receptor, which induce a gain of responsiveness to Activins (non-canonical ligands)
- Activin A induces HO only in *Acvr1*$^{[R206H]}$ mouse models of FOP
- Activin A neutralizing antibody (REGN2477) stops heterotopic bone formation in genetic mouse models of FOP

M#	Day -3 (mm³)	Day 0 (mm³)	Week 6 (mm³)
P	29.57	20.53	81.55
A	71.36	23.69	46.45

Green arrows represent site of surgery (at Day 0)
Blue represents heterotopic ossification (HO) at surgery site
Yellow represents unoperated heterotopic ossification (HO)



Flare-ups of soft tissue preceding formation of heterotopic bone



Guiding Principles

① Leverage multiple approaches to maximize opportunities for gene discovery
- Large general populations
- Mendelian genetics and families
- Founder populations
- Disease cohorts with deep phenotyping

② Depth of phenotypic data, including longitudinal data and quantitative traits

③ Emphasis on large effect coding variation

④ Advantages of multi-ethnic cohorts (e.g. PCSK9 and APOL1)

⑤ Analytical strategies to interrogate wide ranging biological questions

Challenges

① Power to detect rare variant associations; even more challenging for less prevalent diseases

② Large data sets often required for replication of novel gene discoveries

③ Rare variant interpretation, particularly missense and non-coding mutations

④ Methods to handle emerging computational challenges with large datasets and rare variants

⑤ Must develop capabilities for biological and clinical validation

Acknowledgements

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