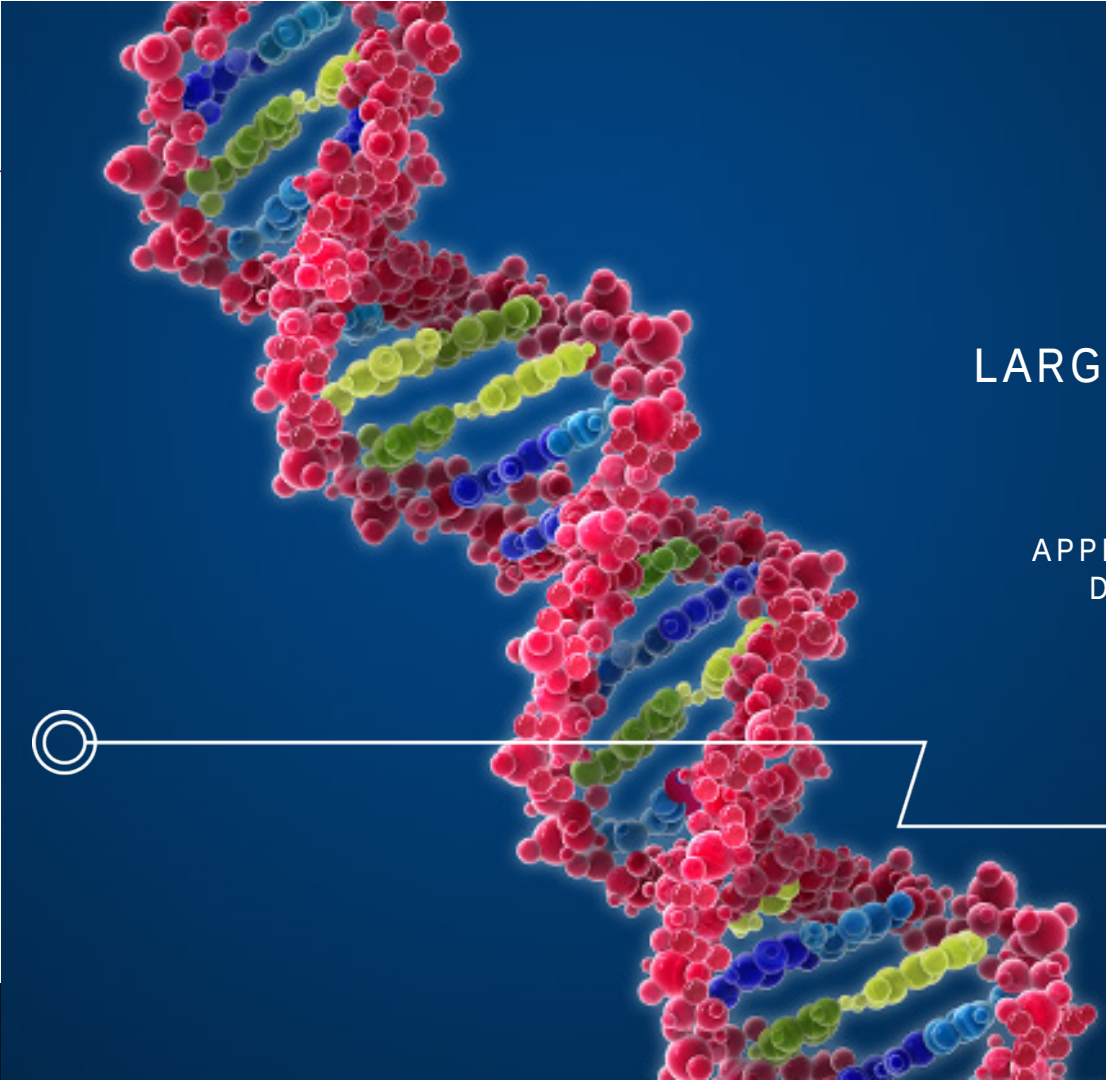


REGENERON
SCIENCE TO MEDICINE®

LARGE SCALE HUMAN GENETICS AT REGENERON

APPLYING HUMAN GENETICS TO DRUG DISCOVERY AND DEVELOPMENT

JEFFREY G. REID, PH.D.
HEAD OF GENOME INFORMATICS
REGENERON PHARMACEUTICALS

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

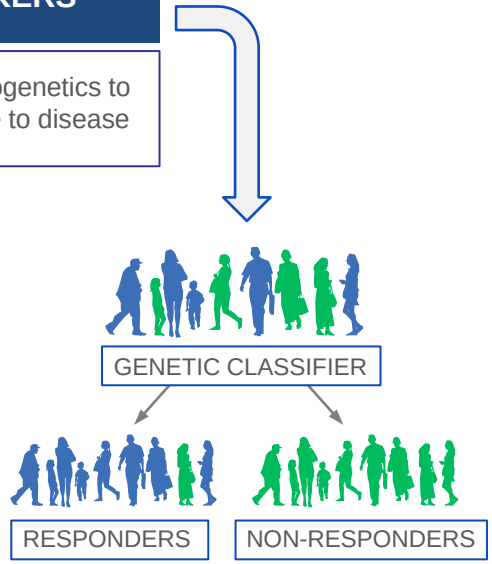
HUMAN GENETICS

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* & deep biology
- ✓ Genetics-guided drug development improves efficiency, timelines, and probability of success

REGENERON GENETICS CENTER: INNOVATIVE TECHNOLOGIES ENABLE ULTRA HIGH-THROUGHPUT SEQUENCING & ANALYSIS

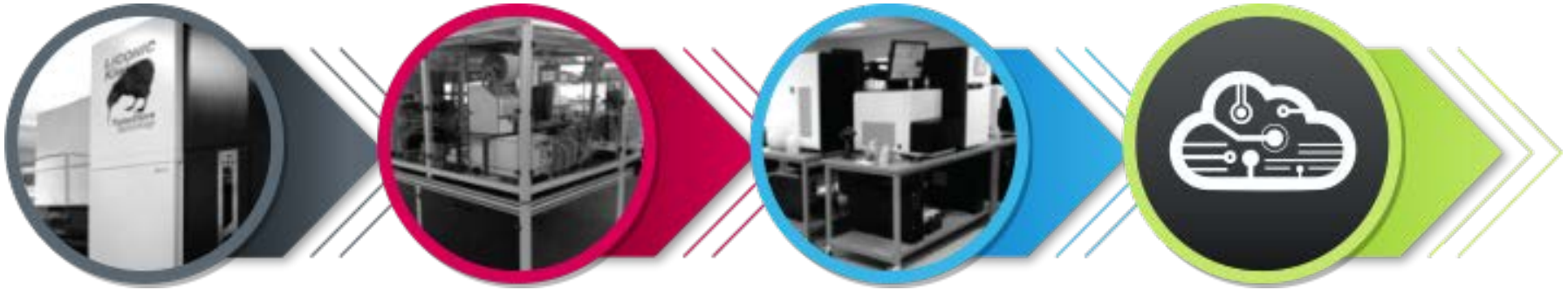
REGENERON®
GENETICS CENTER

AUTOMATED BIOBANK (1.4M SAMPLES)

LIBRARY PREP AUTOMATION (>200,000 SAMPLES/YR)

ILLUMINA FLEET (>200,000 EXOMES/YR)

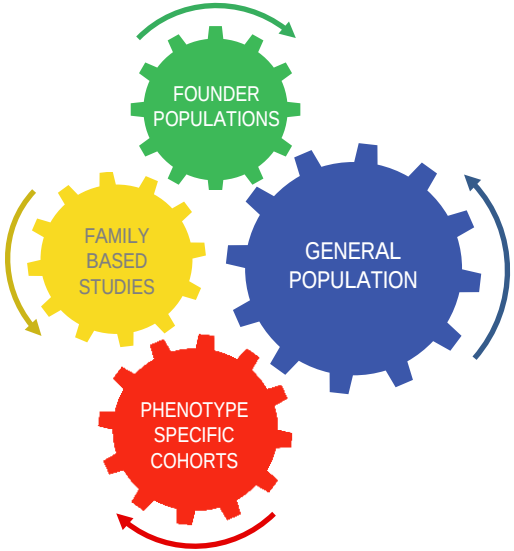
100% CLOUD-BASED INFORMATICS & ANALYSIS



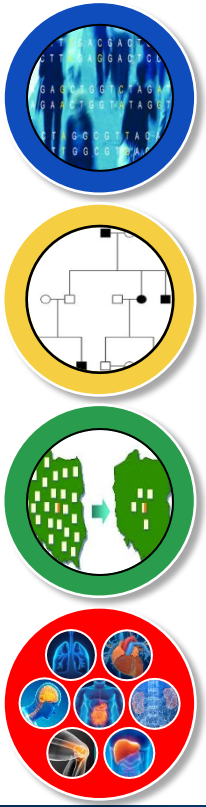
Goal: build the world's most comprehensive genotype-phenotype resource to guide drug discovery & development

BREADTH OF HUMAN GENETICS RESOURCES: RGC NETWORK OF 40+ COLLABORATORS REPRESENTING OVER 1 MILLION SAMPLES

Synergistic efforts across approaches and phenotypes. . .



. . . will fuel genomic discovery



General Population

Geisinger

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LABioMed

Lund University

Family Studies

The University of Iowa

RAMBAM Medical Center

Columbia University Medical Center

SickKids

Children's National Medical Center

Mario Negri Istituto di Ricerche Farmacologiche

Schneider Children's Medical Center of Israel

Baylor College of Medicine

NIH National Institutes of Health

Founder Populations

CNCD Center for Non Communicable Diseases

NIH National Institute of Diabetes and Digestive and Kidney Diseases

ECOGENE-21

University of Maryland Medical Center

Clinic For Special Children
TREATING THE WHOLE CHILD

Phenotype Specific Cohorts

Mayo Clinic

Duke University

UT Southwestern Medical Center

Feinstein Institute for Medical Research
Northwell Health

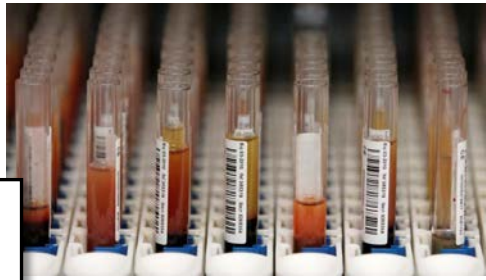
University of Utah Health Care

UConn Health Center

Penn Medicine

RGC COLLABORATION WITH UK BIOBANK: RGC WILL SEQUENCE 500,000 PARTICIPANTS OVER 3-5 YEARS IN MASSIVE SEQUENCING STUDY

REGENERON®
GENETICS CENTER



biobank uk
Improving the health of future generations

Mar 22, 2017

U.K. BIOBANK, REGENERON AND GSK ANNOUNCE LARGEST GENE SEQUENCING INITIATIVE ON WORLD'S MOST DETAILED HEALTH DATABASE TO IMPROVE DRUG DISCOVERY AND DISEASE DIAGNOSIS

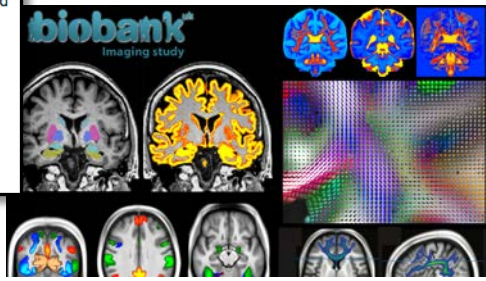
Groundbreaking UK/US Initiative Will Deliver First Data Within a Year

TARRYTOWN, N.Y., March 22, 2017 /PRNewswire/ – Regeneron Pharmaceuticals, Inc. (NASDAQ: **REGN**), today announced a major research initiative among the Regeneron Genetics Center (RGC), U.K. Biobank and GSK to generate genetic sequence data from the 500,000 volunteer participants in the U.K. Biobank resource. The initiative will enable researchers to gain valuable insights to support advances in the development of new medicines for a wide range of serious and life threatening diseases.

Genetic evidence has revolutionized scientific discovery and drug development in recent years by providing clear links between genes and disease. Currently, an estimated 90% of potential medicines entering clinical trials fail to demonstrate the necessary efficacy and safety, and never reach patients. Many of these failures are due to an incomplete understanding of the link between the biological target of a drug and human disease. By contrast, medicines developed with human genetic evidence have had substantially higher success rates and patient care has benefited.

U.K. Biobank is the world's most comprehensive health resource. It has been collecting information and samples from its 500,000 participants for the past ten years, and ensures that data provided to health researchers does not identify them. RGC and GSK have committed an initial investment to enable the sequencing of the first 50,000 samples, to be completed before the end of 2017. Sequencing of U.K. Biobank's samples will be performed at the RGC facility, one of the world's largest human genetics sequencing centers. Sequencing of the full 500,000 samples in U.K. Biobank is expected to take three to five years.

gsk



NOVEL GENETIC DISCOVERIES SUPPORTING REGENERON'S EVINACUMAB (ANGPTL3 ANTIBODY) PROGRAM FOR DYSLIPIDEMIAS AND CV DISEASE

March 2016

The NEW ENGLAND JOURNAL of MEDICINE

Carriers of Inactivating mutations in ANGPTL4 have ~30-70% lower risk of CAD


Inactivating Variants in *ANGPTL4* and Risk of Coronary Artery Disease

March 2017

JAMA
The Journal of the American Medical Association

LOF and damaging mutations in LPL associated with ~85% increased risk of CAD


Association of Rare and Common Variation in the Lipoprotein Lipase Gene With Coronary Artery Disease

May 2017

The NEW ENGLAND JOURNAL of MEDICINE

LOF mutations in ANGPTL3 confer >40% reduction in risk of CAD


Genetic and Pharmacologic Inactivation of ANGPTL3 and Cardiovascular Disease

ANGPTL4 ⊣ **LPL** ↑ activity → decreased CAD risk; ↓ activity → increased CAD risk ⊣ **ANGPTL3**

↓ activity → decreased CAD risk

↓ activity → decreased CAD risk

Genetic results found

MyCode researchers expect that 1 in every 25 participants, or 4 percent of those signing up, will have a genetic mutation indicating a health risk. Because of the lengthy analysis process, results are just starting to be reported. As of August 2016, patients have heard about these results.

Condition	Number of patients receiving results
Hereditary breast and ovarian cancer (BRCA1 and BRCA2) early breast, ovarian, prostate, other cancers	79
Familial hypercholesterolemia (FH) early heart attacks, strokes	29
Lynch syndrome early colon, uterine, other cancers	16
Cardiomyopathy heart muscle diseases with dangerous complications	11
Long QT syndrome irregular heartbeat with dangerous complications	4
Malignant hyperthermia life-threatening, triggered by certain anesthesia drugs	2
Arrhythmogenic right ventricular cardiomyopathy heart muscle disease with dangerous complications, different genetics than other cardiomyopathies	4
Multiple endocrine neoplasia type 2 early thyroid cancer	2
Tuberous sclerosis non-cancerous tumors	1
Hereditary pheochromocytomas and paragangliomas tumors of the adrenal gland	1
Total	149

GEISINGER'S RETURN OF RESULTS PROGRAM: APPROX. 1 IN 25 PARTICIPANTS HAS ACTIONABLE GENETICS FINDINGS

Barbara Barnes's MyCode Story

- Barbara Barnes: 57 year old grandmother raising three grandchildren, ages, 3, 5, and 14
- Found to have a pathogenic mutation in BRCA1, increasing breast and ovarian cancer risk
- "Ok, so what do we do next? I have 15 more years to go until they're raised."
  - Genetic counseling and follow up care at Geisinger
  - Preventative surgical removal of ovaries and fallopian tubes
  - Found stage 1 cancer in a fallopian tube, completing chemo with expected excellent outcome
  - "If I hadn't been in MyCode, I wouldn't have known."