The Path to Precision Medicine: From Discovery to Patient Care

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REGENERON™ GENETICS CENTER

The Reality of Therapeutic Development in 2017

- Despite increased investment in R+D in the pharmaceutical industry, the number of new molecular entities is not increasing
- >90% of molecules that enter Phase I clinical trials fail to demonstrate sufficient safety and efficacy to gain regulatory approval
- Most failures occur in Phase II clinical trials
  - 50% due to lack of efficacy
  - 25% due to toxicity
- Pre-clinical models may be poor predictors of clinical benefit
- *Compounds supported by human genetics evidence are substantially more likely to succeed*

The Power of Human Genetics to Accelerate Target Identification, Validation and Drug Development

2003


Mutations in *PCSK9* cause autosomal dominant hypercholesterolemia

Family studies identify PCSK9 GOF as a causal FH gene

2006

Population studies identify PCSK9 LOF variants conferring ~88% reduction in CHD

2012

Clinical proof of concept

2008


A Null Mutation in Human *APOC3* Confers a Favorable Plasma Lipid Profile and Apparent Cardioprotection

Null APOC3 mutation enriched in Amish points to cardio-protective effects

2014

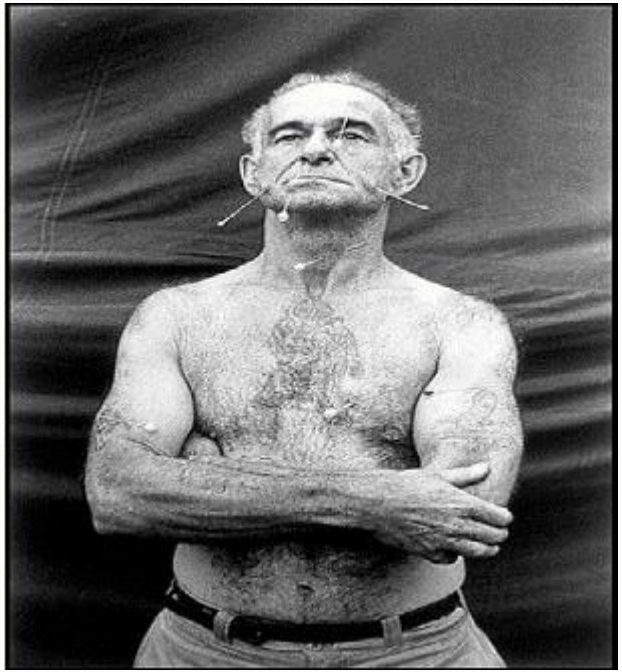
Two population studies identify variants conferring ~40% reduction in CHD

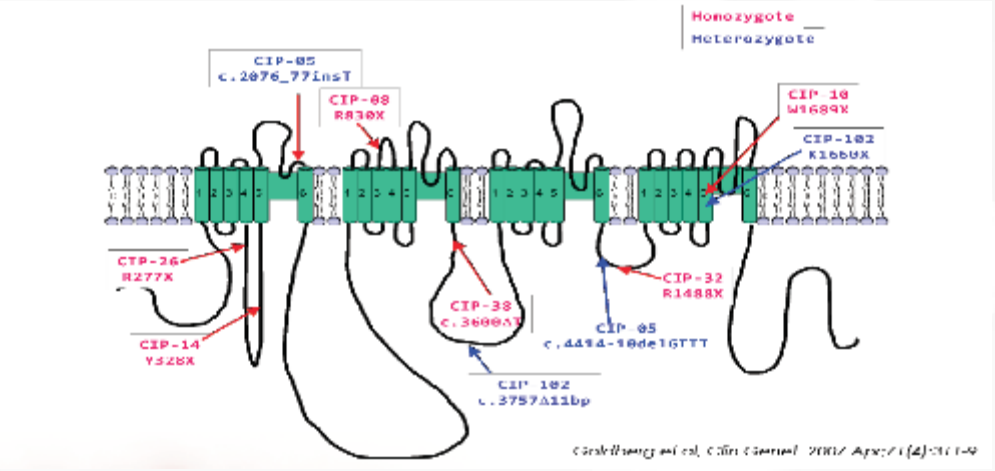
2015


Targeting APOC3 in the Familial Chylomicronemia Syndrome

Clinical proof of concept

Congenital Insensitivity to Pain (CIP) and the *SCN9A* Gene: Human Genetics Provides Insights Into New Pain Drug Targets





- CIP → pain free burns, fractures, childbirth, etc
- Extremely rare: <1/1,000,000 prevalence
- Mutations in *SCN9A* cause insensitivity to pain
- Efforts to mimic the effects of pain insensitivity through therapeutics blocking the corresponding protein are being pursued

Application of Human Genetics to Accelerate Novel Target Identification and Clinical Development

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

"Do Well by Doing Good"

Target Discovery

Identify new drug targets and pathways

Human Genetics

Mouse Genetics

Indication Discovery

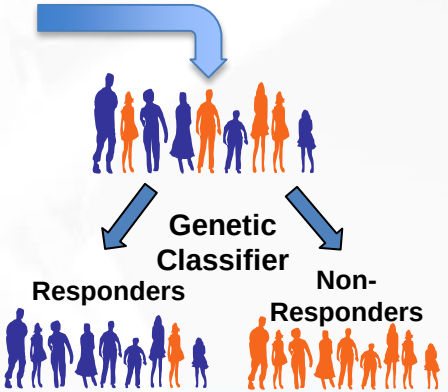
Identify new indications for drug targets and programs

Derisking

Confirm lack of "on-target adverse side effects" in drug target LoF carriers

Biomarker

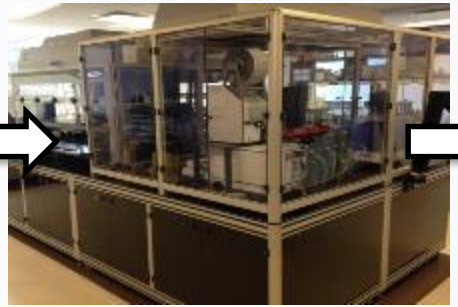
Develop pharmacogenetic markers to predict drug response



Engine Driving Identification of Rare Loss of Function Mutations that Inform Human Biology and Drug Development:

Ultra High-Throughput Sequencing and Analysis at the Regeneron Genetics Center

Automated Biobank (1.4M Samples)	Library Prep Automation (>200,000 Samples/Yr)	Illumina Fleet (>150,000 Exomes/Yr)	Cloud Based Informatics & Analysis



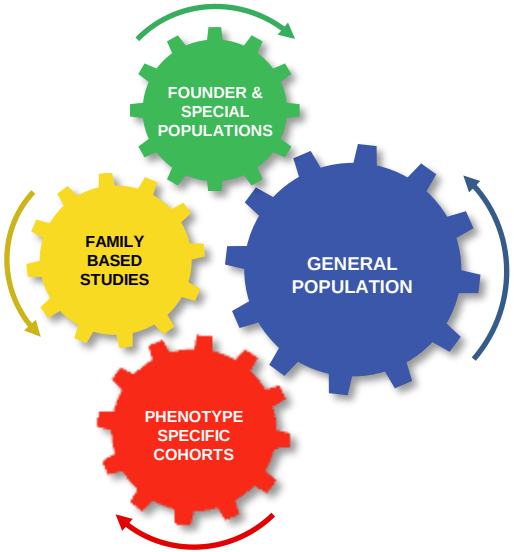
Technologies and Capabilities

- Automated biobank with 1.4M+ sample capacity
- Custom fully-automated exome and targeted sequencing sample preparation workflows
- Currently exome sequencing >2,500 exomes per week
  - >250,000 exomes completed
- Among the first “genome center in the cloud” with fully automated analysis pipelines

Maximizing Discovery Opportunities by Leveraging Human Genetics Resources Across Genetic Trait Architecture and Phenotypes

50+ Academic collaborators – Over 250,000 exomes sequenced

Integrated approaches across genetic trait architectures . . .



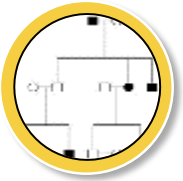
. . . will power genomic discovery

General Population

Geisinger · biobank UK · LABioMed · Lund University

Phenotype Specific Cohorts

Mayo Clinic · Duke · UT Southwestern Medical Center · Feinstein Institute for Medical Research, Northwell Health · University of Utah Health Care · UConn Health Center · Penn



Family Studies

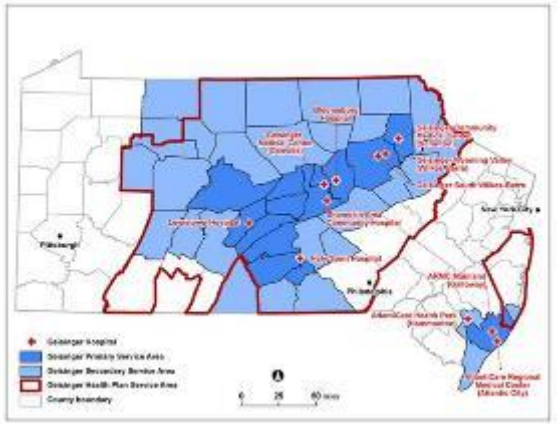
Columbia University Medical Center · BCM Baylor College of Medicine · The University of Iowa · Children's · Mario Negri Istituto di Ricerche Farmacologiche · SickKids · NIH · Clinic for Special Children · DDC · Schneider Children's Medical Center of Israel · RAMBAM Medical Center

Founder & Special Populations

University of Maryland School of Medicine · NIH · NIH · Penn · Global Gene Corp · CNCD · Einstein · Albert Einstein College of Medicine

Geisinger-Regeneron DiscovEHR Collaboration

Two organizations focused on making genomic data medically actionable



Goal: Build comprehensive genotype-phenotype resource combining de-identified genomic and clinical data from >250,000 people to aid drug development and implementation of genomic medicine into patient care

- Geisinger: Integrated health care system
  - 1.6M participants
  - Amongst earliest adopters of EHRs (1996) and leaders in clinical informatics
    - Longitudinal EHR data: Median of ~18 outpatient visits per patient over 13.4 years
- Recruitment ongoing
  - 119,000 patients consented into MyCode-DiscovEHR cohort
  - >90,000 sequenced at the Regeneron Genetics Center
  - 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

Science
AAAS

HUMAN GENETICS

Distribution and clinical impact of functional variants in 50,726 whole-exome sequences from the DiscovEHR study

Frederick E. Dewey,[1]* Michael F. Murray,[2] John D. Overton,[1] Lukas Habegger,[1] Joseph B. Leader,[2] Samantha N. Fetterolf,[2] Colm O'Dushlaine,[1] Cristopher V. Van Hout,[1] Jeffrey Staples,[1] Claudia Gonzaga-Jauregui,[1] Raghu Metpally,[2] Sarah A. Pendergrass,[2] Monica A. Giovanni,[2] H. Lester Kirchner,[2] Suganthi Balasubramanian,[1] Noura S. Abul-Husn,[1] Dustin N. Hartzel,[2] Daniel R. Lavage,[2] Korey A. Kost,[2] Jonathan S. Packer,[1] Alexander E. Lopez,[1] John Penn,[1] Semanti Mukherjee,[1] Nehal Gosalia,[1] Manoj Kanagaraj,[1] Alexander H. Li,[1] Lyndon J. Mitnaul,[1] Lance J. Adams,[2] Thomas N. Person,[2] Kavita Praveen,[1] Anthony Marcketta,[1] Matthew S. Lebo,[3] Christina A. Austin-Tse,[3] Heather M. Mason-Suares,[3] Shannon Bruse,[1] Scott Mellis,[4] Robert Phillips,[4] Neil Stahl,[4] Andrew Murphy,[4] Aris Economides,[1] Kimberly A. Skelding,[2] Christopher D. Still,[2] James R. Elmore,[2] Ingrid B. Borecki,[1] George D. Yancopoulos,[4] F. Daniel Davis,[2] William A. Faucett,[2] Omri Gottesman,[1] Marylyn D. Ritchie,[2] Alan R. Shuldiner,[1] Jeffrey G. Reid,[1] David H. Ledbetter,[2] Aris Baras,[1] David J. Carey[2]*

The DiscovEHR collaboration between the Regeneron Genetics Center and Geisinger Health System couples high-throughput sequencing to an integrated health care system using longitudinal electronic health records (EHRs). We sequenced the exomes of 50,726 adult participants in the DiscovEHR study to identify ~4.2 million rare single-nucleotide variants and insertion/deletion events, of which ~176,000 are predicted to result in a loss of gene function. Linking these data to EHR-derived clinical phenotypes, we find clinical associations supporting therapeutic targets, including genes encoding drug targets for lipid lowering, and identify previously unidentified rare alleles associated with lipid levels and other blood level traits. About 3.5% of individuals harbor deleterious variants in 76 clinically actionable genes. The DiscovEHR data set provides a blueprint for large-scale precision medicine initiatives and genomics-guided therapeutic discovery.

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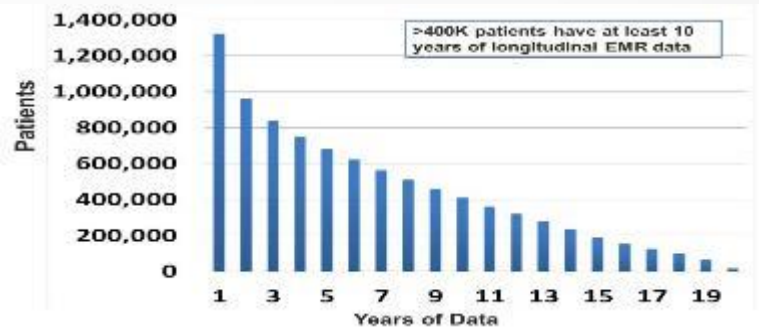
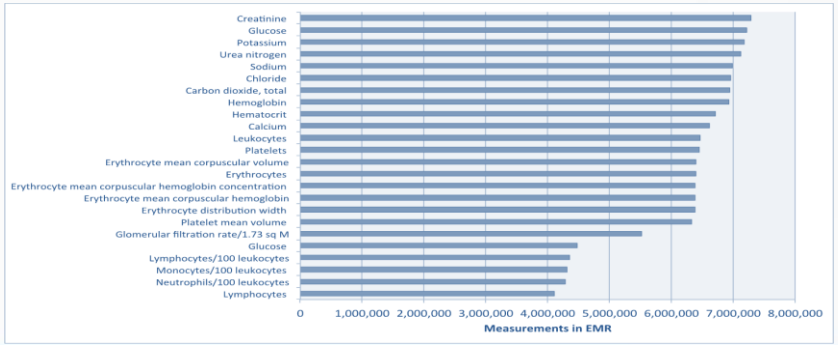
In-Depth, Longitudinal Health Records Enriched for Age-Related Diseases and Phenotypes

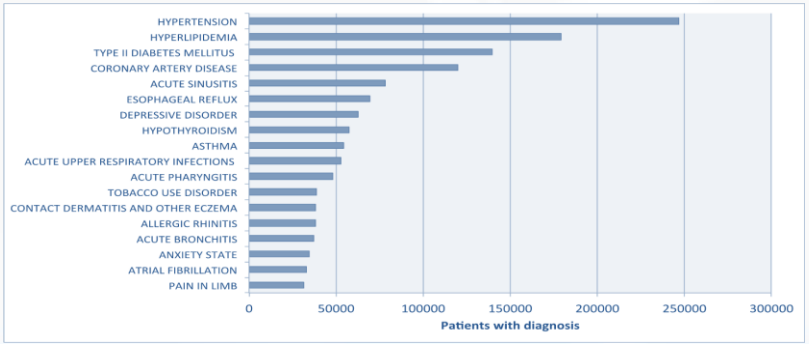
Patients by Years of Clinical Data



Most Prevalent Labs in GHS EHR

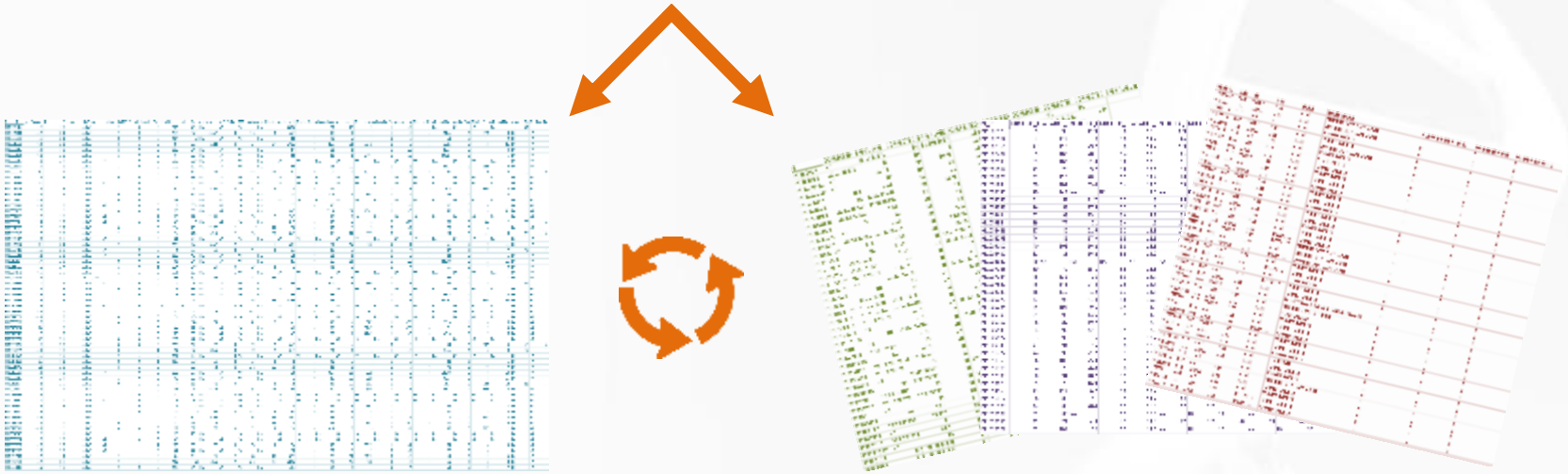


Most Prevalent Office Visit Dx in GHS EHR



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

A constantly growing library of more than 8,000 quantitative and binary traits are available for high-throughput and in-depth genotype-first and phenotype-first analyses:



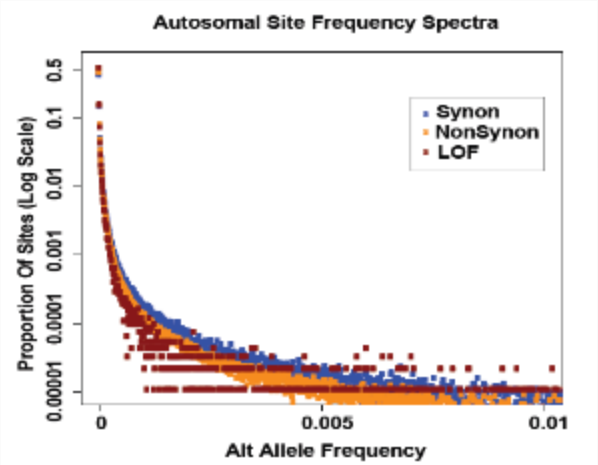
Binary and Quantitative Trait Matrices:

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

Sequence Variants Identified Using Whole Exome Sequencing of 50,726 DiscovEHR Participants *(Dewey et al, Science 2016)*



In 50K Exomes:

- *92% (n=17,409) of genes with at least 1 heterozygous pLOF*
- *7% (n=1,313) of genes with at least 1 homozygous pLOF*

Each individual :

- *Heterozygous pLOF for ~21 genes*
- *Homozygous pLOF for ~1 gene*

Variant type	All variants	Allele frequency ≤ 1%
Single nucleotide variants	4,028,206	3,947,488
Insertion/deletion variants	224,100	218,785
Predicted loss of function variants	176,365	175,393
Nonsynonymous variants	2,025,800	2,002,912
Total	4,252,306	4,166,273

Proof-of-principle: DiscovEHR Genetics Predict Efficacy of Established Targets for Hyperlipidemia *(Dewey et al, Science 2016)*

						LDL-c		HDL-c		Triglycerides		Total cholesterol	
Target	Agent	Action	Phase	Clinical effect	LOF carriers	p	effect	p	effect	p	Effect	p	effect
PPARA	Fenofibrate	Agonist	Approved	Decreased triglycerides, increased HDL	2	0.8	9 mg/dl	0.2	-28%	0.09	113%	0.4	27 mg/dl
HMGCR	Atorvastatin, rosuvastatin, pravastatin, simvastatin	Antagonist	Approved	Decreased LDL, total cholesterol, increased HDL	12	0.7	-4 mg/dl	0.3	9%	0.6	-8%	0.7	-4 mg/dl
NPC1L1	Ezetemibe	Antagonist	Approved	Decreased LDL	121	0.03	-7 mg/dl	0.07	-4%	0.5	-3%	0.0004	-12 mg/dl
APOB	Mipomersen	Antagonist	Approved	Decreased LDL	80	0.0003	-15 mg/dl	0.06	6%	0.002	-15%	$8.x10^{-7}$	-21 mg/dl
MTTP	Lomitapide	Antagonist	Approved	Decreased LDL	24	0.9	1 mg/dl	0.4	4%	0.7	3%	1.0	0.2 mg/dl
HCAR3	Niacin	Agonist	Approved	Increased HDL, decreased triglycerides, LDL	107	0.4	-3 mg/dl	0.4	-2%	0.5	4%	0.3	-4 mg/d;
CETP	Anacetrapib, evacetrapib	Antagonist	Phase 3	Increased HDL	37	0.3	-6 mg/dl	$2.0x10^{-6}$	23%	0.6	5%	0.1	9 mg/dl
PCSK9	Alirocumab, evolocumab, bococizumab	Antagonist	Phase 3	Decreased LDL	52	$8.8x10^{-9}$	-25 mg/dl	0.3	3%	0.03	-12%	$6.4x10^{-6}$	-21 mg/dl
APOC3	APOC3 inhibitors	Antagonist	Phase 2	Decreased triglycerides, increase HDL	226	0.3	-3 mg/dl	$1.5x10^{-43}$	28%	$1.5x10^{-87}$	-48%	0.2	-4 mg/dl
ACLY	ATP citrate lyase inhibitors	Antagonist	Phase 2	Decreased LDL	13	0.2	-14 mg/dl	1.0	0%	0.3	-13%	0.4	-10 mg/dl
ANGPTL3	ANGPTL3 inhibitors	Antagonist	Phase 2	Decreased triglycerides, LDL, HDL	150	0.0004	-10 mg/dl	0.0002	-8%	$6.4x10^{-15}$	-27%	$1.6x10^{-10}$	-19 mg/dl

8/11 Lipid therapy targets harbor LOFs with nominally significant or directionally consistent clinical associations that recapitulate drug effects

DiscovEHRy of New Drug Targets

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

Frederick E. Dewey, M.D., Viktoria Gusarova, Ph.D., Colm O'Dushlaine, Ph.D., Omri Gottesman, M.D., Jesus Trejos, M.S., Charleen Hunt, Ph.D., Cristopher V. Van Hout, Ph.D., Lukas Habegger, Ph.D., David Buckler, Ph.D., Ka-Man V. Lai, Ph.D., Joseph B. Leader, Ph.D., Michael F. Murray, M.D., Marylyn D. Ritchie, Ph.D., H. Lester Kirchner, Ph.D., David H. Ledbetter, Ph.D., John Penn, M.S., Alexander Lopez, M.S., Ingrid B. Borecki, Ph.D., John D. Overton, Ph.D., Jeffrey G. Reid, Ph.D., David J. Carey, Ph.D., Andrew J. Murphy, Ph.D., George D. Yancopoulos, M.D., Ph.D., Aris Baras, M.D., Jesper Gromada, Ph.D., D.M.Sc., and Alan R. Shuldiner, M.D.

March 3, 2016

Loss-of-Function Carriers in a *ANGPTL4* Have Favorable Lipid Phenotypes and Are Protected From CAD *(Dewey et al, NEJM 2016)*

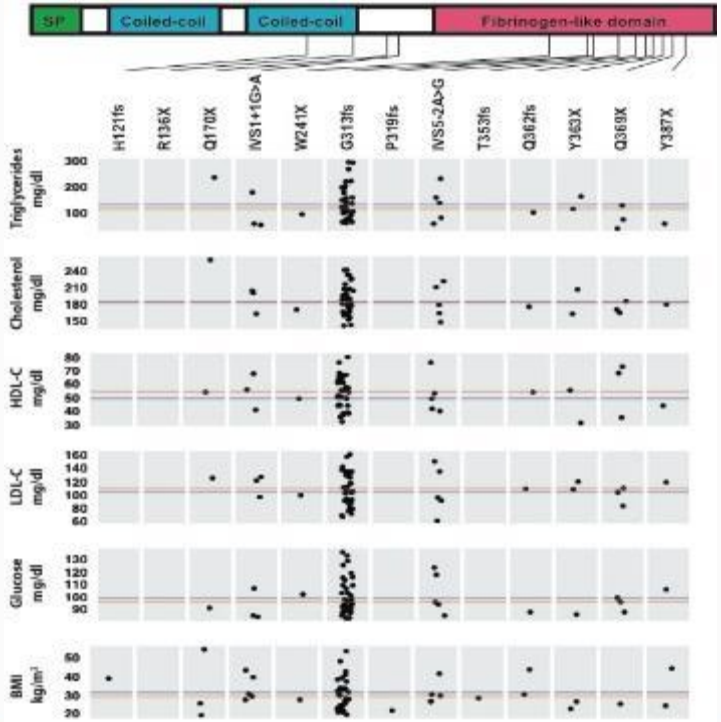


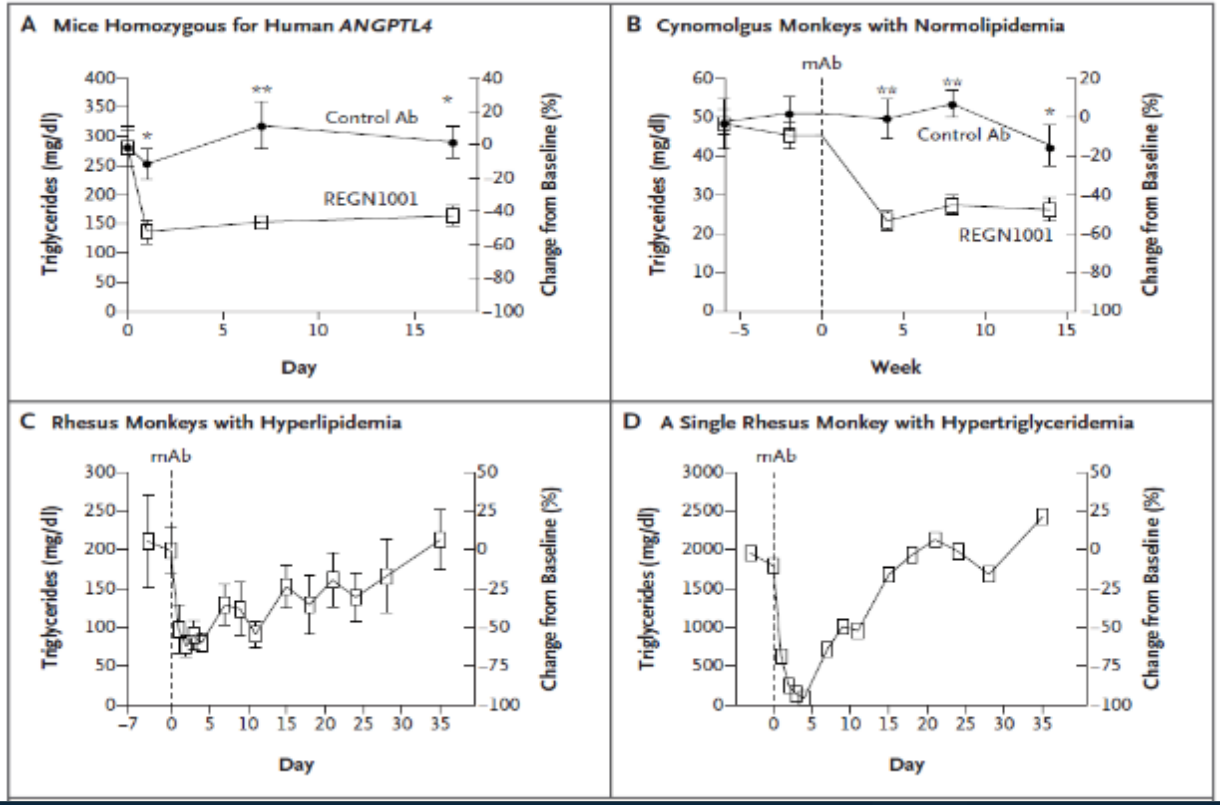
Table 2. Association between *ANGPTL4* E40K or Other Inactivating Mutations and Lipid Levels.*

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

Hypolipidemic Effects of Anti-ANGPTL4 Antibody in Mice and Monkeys *(Dewey et al, NEJM 2016)*



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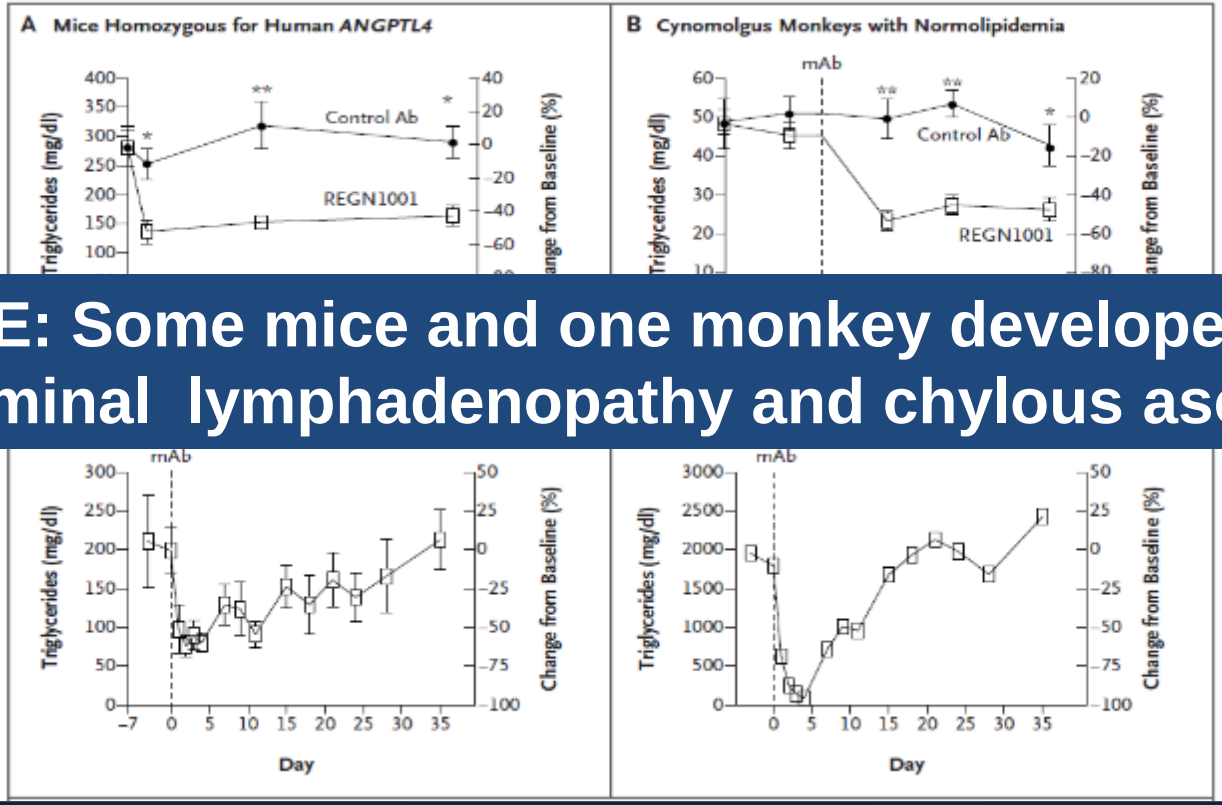


AE: Some mice and one monkey developed abdominal lymphadenopathy and chylous ascities

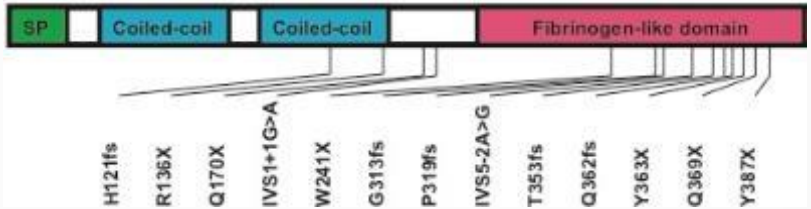
ANGPTL4 p.E40K Human Homozygotes do not Exhibit Increased Rates of Lymphatic Abdominal Pathology in DiscovEHR

In chart review of 17 p.E40K homozygotes, 5 had CT abdominal imaging, and 4/5 had explicit mention of normal abdominal lymphatics, 1/5 had no mention of lymphatic abnormalities

Phenotype	Non-carriers (n=41,777)	E40/K40 heterozygotes (n=1,661)		K40 homozygotes (n=17)		pLOF carriers (n=75)	
	N (%)	N (%)	P*	N (%)	P*	N (%)	P*
Disorders of lymphoid system	3,831 (9.2)	154 (9.3)	0.9	1 (5.9)	0.7	5 (6.7)	0.6
Disorder of lymph node	1,661 (4.0)	70 (4.2)	0.7	0 (0.0)	0.7	1 (1.3)	0.4
Lymphadenitis	295 (7.1)	12 (7.2)	0.9	0 (0.0)	0.7	0 (0.0)	1.0
Mesenteric lymphadenitis	12 (0.03)	0 (0.0)	0.5	0 (0.0)	0.9	0 (0.0)	0.9
Granulomatous lymphadenitis	5 (0.01)	0 (0.0)	0.7	0 (0.0)	1.0	0 (0.0)	0.9
Ascites	308 (0.7)	11 (0.7)	0.8	1 (5.9)	0.1	2 (2.7)	0.2
Peritonitis	282 (0.7)	17 (1.0)	0.1	0 (0.0)	0.7	2 (2.7)	0.2
Malabsorption	3,291 (7.9)	142 (8.6)	0.3	0 (0.0)	0.3	8 (10.7)	0.5
Abdominal discomfort	15,183 (36.3)	612 (37.0)	0.2	4 (35.2)	0.6	17 (22.7)	0.03
Diarrhea symptom	6,099 (14.6)	222 (13.4)	0.2	2 (10.2)	0.7	11 (14.7)	1.0

*Versus sequenced non-carriers

ANGPTL4 p.E40K and Loss of Function Variants are Associated with Reduced Odds of Type 2 Diabetes: A new indication for ANGPTL4 inhibition?



Diabetes														Total
Cases	0	0	0	1	0	6	0	2	0	0	0	0	1	10/9,948
Controls	1	1	3	3	1	33	1	4	1	2	2	3	0	55/26,198

- **Take home points:**
  - The p.E40K variant was associated with ~15% reduced odds of diabetes per allele
  - Loss of function variant carriers had 58% reduced odds of diabetes

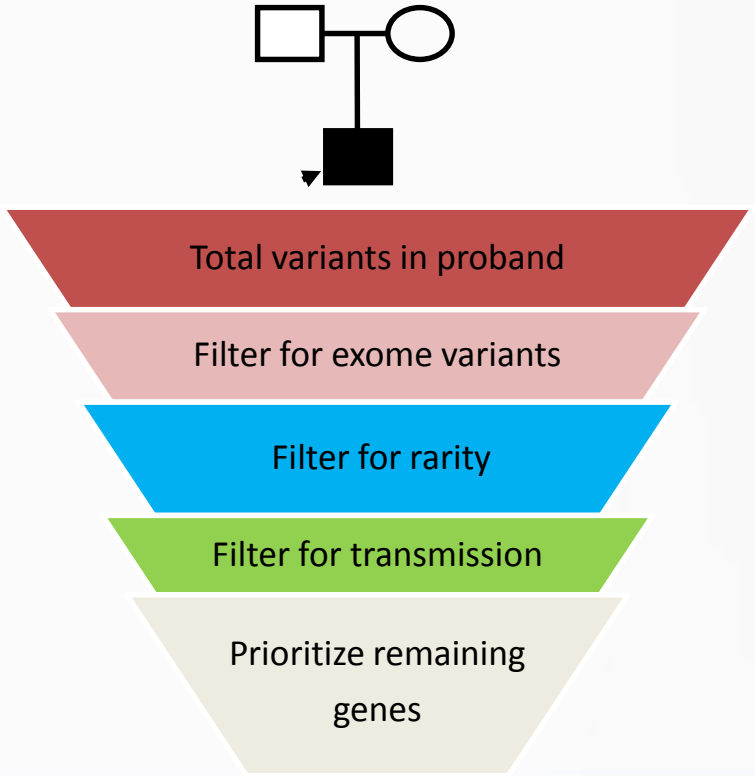
the	p.E40K (n = 1,661 heterozygotes and 17 homozygotes)				Heterozygous loss-of-function variants (n = 75)			
Disease	**Allele Frequency: Cases**	**Allele Frequency: Controls**	**Odds Ratio* (95% CI)**	**P***	**Allele Frequency: Cases**	**Allele Frequency: Controls**	**Odds Ratio* (95% CI)**	**P***
Type 2 diabetes	1.84 (355 hets, 6 homs)	2.06 (1,053 hets, 14 homs)	0.86 (0.76-0.99)	0.03	0.05 (10 hets)	0.11 (58 hets)	0.42 (0.19-0.83)	0.01

Abbreviations: AF, allele frequency; hets, heterozygotes; homs, homozygotes; CAF, cumulative allele frequency; OR, odds ratio

*Adjusted for age, age^2, sex, principal components of ancestry, and BMI.

O'Dushlaine, et al. ,in preparation

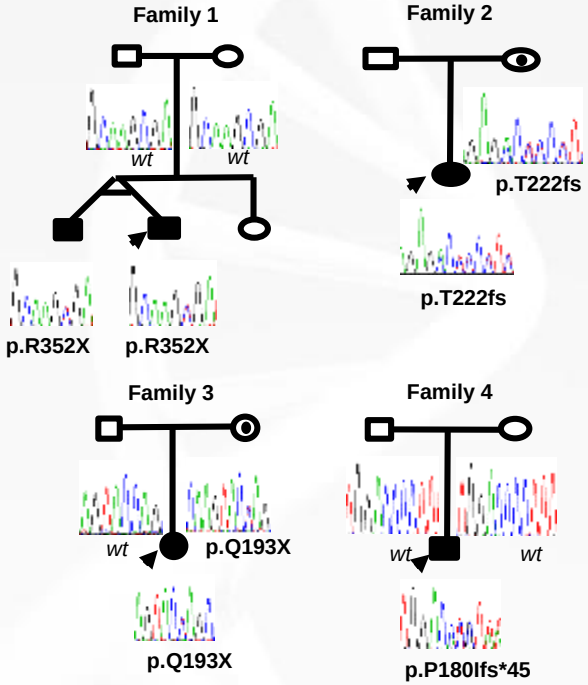
Insights From Whole Exome Sequencing in Mendelian Diseases Collaborations (CUMC, CSC & TSK)



Families/samples sequenced	756/5747
Families/samples analyzed	395/2049
Families with known causative variants	23 (15)
Families with novel variants in known disease genes	92 (32)
Families with novel disease genes	126
Families with multiple candidate genes	153

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

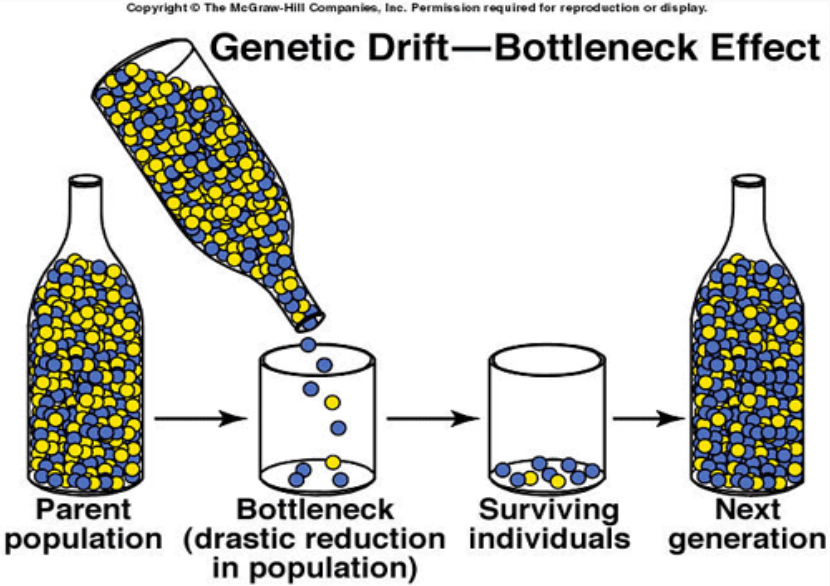
Family/Proband ID	VARIANT	INHERITANCE	DELETERIOUS PREDICTION	GHS ALLELE FREQUENCY
Family 1	c.C1054T; p.R352X	*de novo*	damaging	0
Family 2	c.664delA; p.T222fs	maternal	damaging	0
Family 3	c.C577T; p.Q193X	maternal	damaging	0
Family 4	c.537_546del; p.P180Ifs*45	*de novo*	damaging	0
Family 5	c.1070_1070 delC; p.S359Lfs*20	*de novo*	damaging	0
Family 6	c.C293G; p.P98R	*de novo*	damaging	0
Family 7	c.1115dupC; p.Pro372fs	paternal	damaging	0
Family 8	c.498_500delCTC; p.166_167delS	paternal	damaging	0
Singleton 1	c.702+1G>A (splicing)	unknown	damaging	0
Singleton 2	25.9kb deletion	unknown	damaging	0



- ~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)

Claudia Gonzaga-Jauregui and Wendy Chung

Founder Populations: Stacking the Deck for Discovery of Novel Genes for Aging and Age-Related Phenotypes



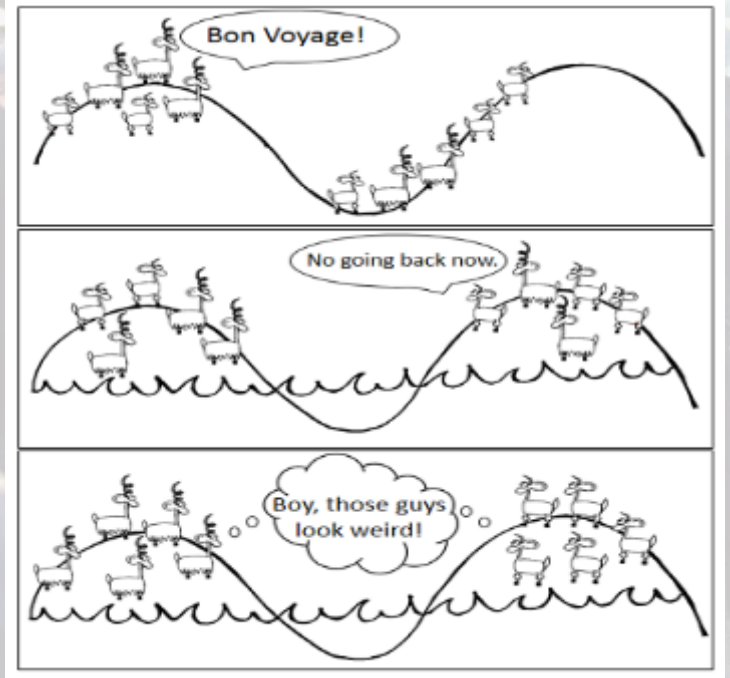
- **Principle 1: Genetic Homogeneity:**
  - Gene pool of entire population derives from a small number of founders
- **Principle 2: Drift:**
  - Rare (single copy) founder LOF alleles can increase in frequency
    - Opportunity for novel large-effect gene discovery
    - Opportunities to identify modifier genes
- **Principle 3: Consanguinity and large families:**
  - Further opportunity to identify homozygotes for enriched LOF alleles
- **Principle 4: Homogeneous lifestyle**
  - Fewer confounding influences
  - Geographically localized → Genotype-first call-back studies

Why Study Complex Diseases in the Amish?

Why Study Complex Diseases in the Amish?

- A cultural isolate – traditional dress, no electricity, phones, cars
- Genetically homogeneous closed founder population

Why Study Complex Diseases in the Amish?



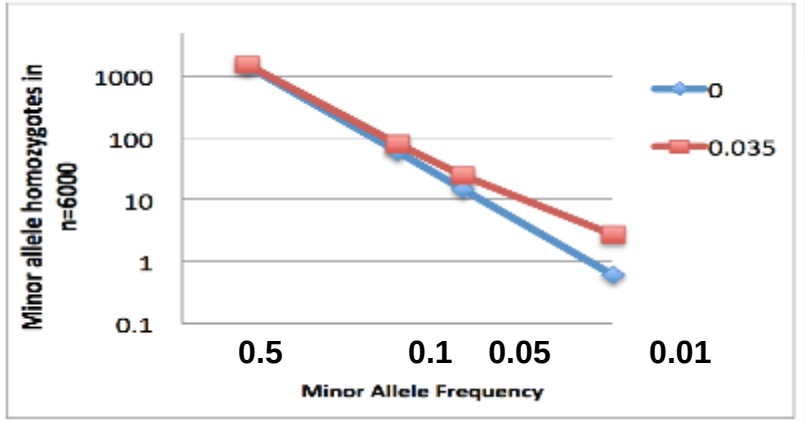
- A cultural isolate – traditional dress, no electricity, phones, cars
- Genetically homogeneous closed founder population
  - Complex genetics less complex
  - Enrichment of rare large-effect mutations (founder effect)
- Western/Central European in origin

Why Study Complex Diseases in the Amish?

- A cultural isolate – traditional dress, no electricity, phones, cars
- Genetically homogeneous closed founder population
  - Complex genetics less complex
  - Enrichment of rare large-effect mutations (founder effect)
- Western/Central European in origin
- Very large extended pedigrees (mean sibship size = 7)
  - Extensive genealogical records (Fisher Book, AGD)
  - Geographically localized
- Homogeneous lifestyle (e.g., diet, minimal use of medications)
- Generalizability of findings

Old Order Amish Demography has Increased the Number of Some Minor Allele Homozygotes

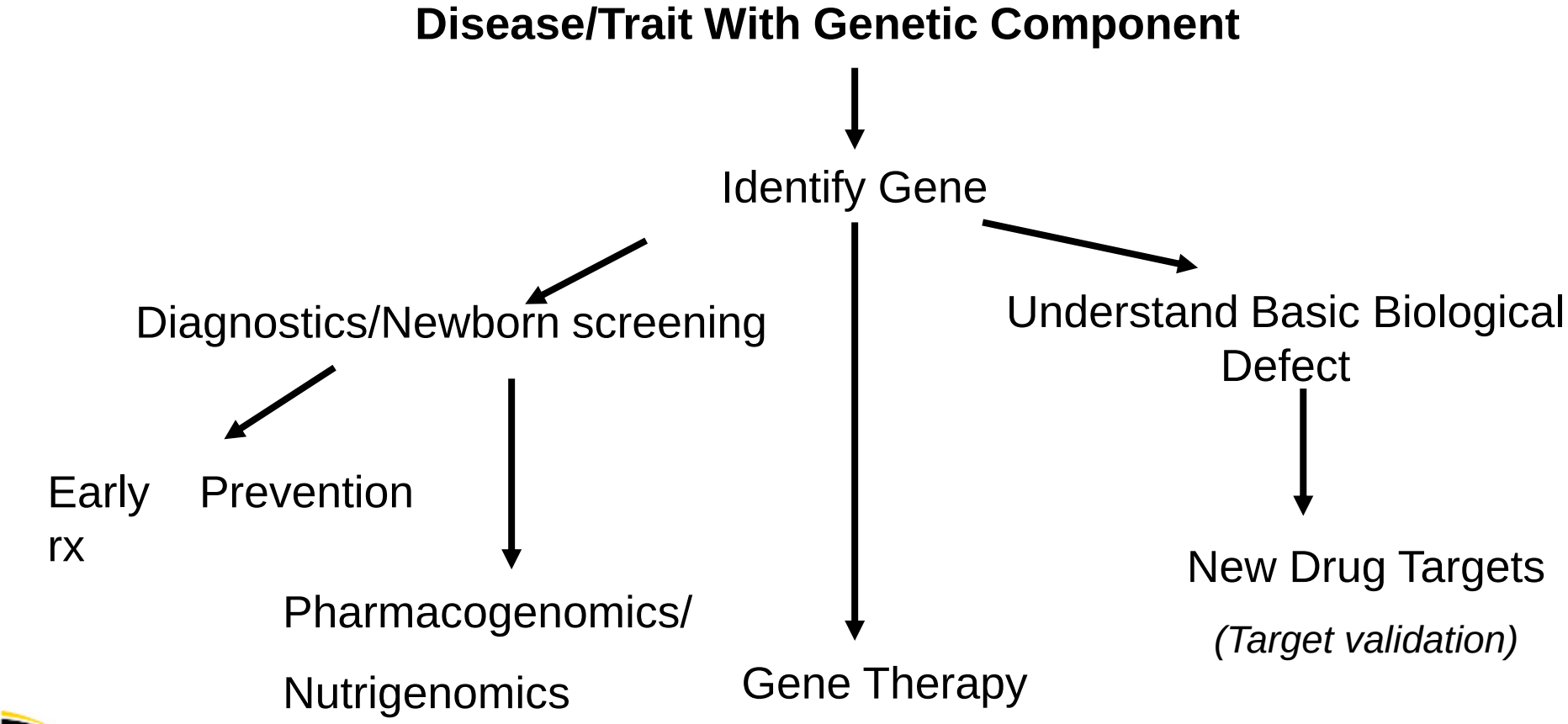
- Alleles have drifted to higher frequency in the Amish, R3527Q *APOB*; R19X *APOC3*, L28P *DRK1B*, etc.
- Finite population size results in consanguinity, ~3.5% of each Amish genome is autozygous
- Example: allele drifts from 1% to 5% in the Amish, ~40 fold increase in minor allele homozygotes



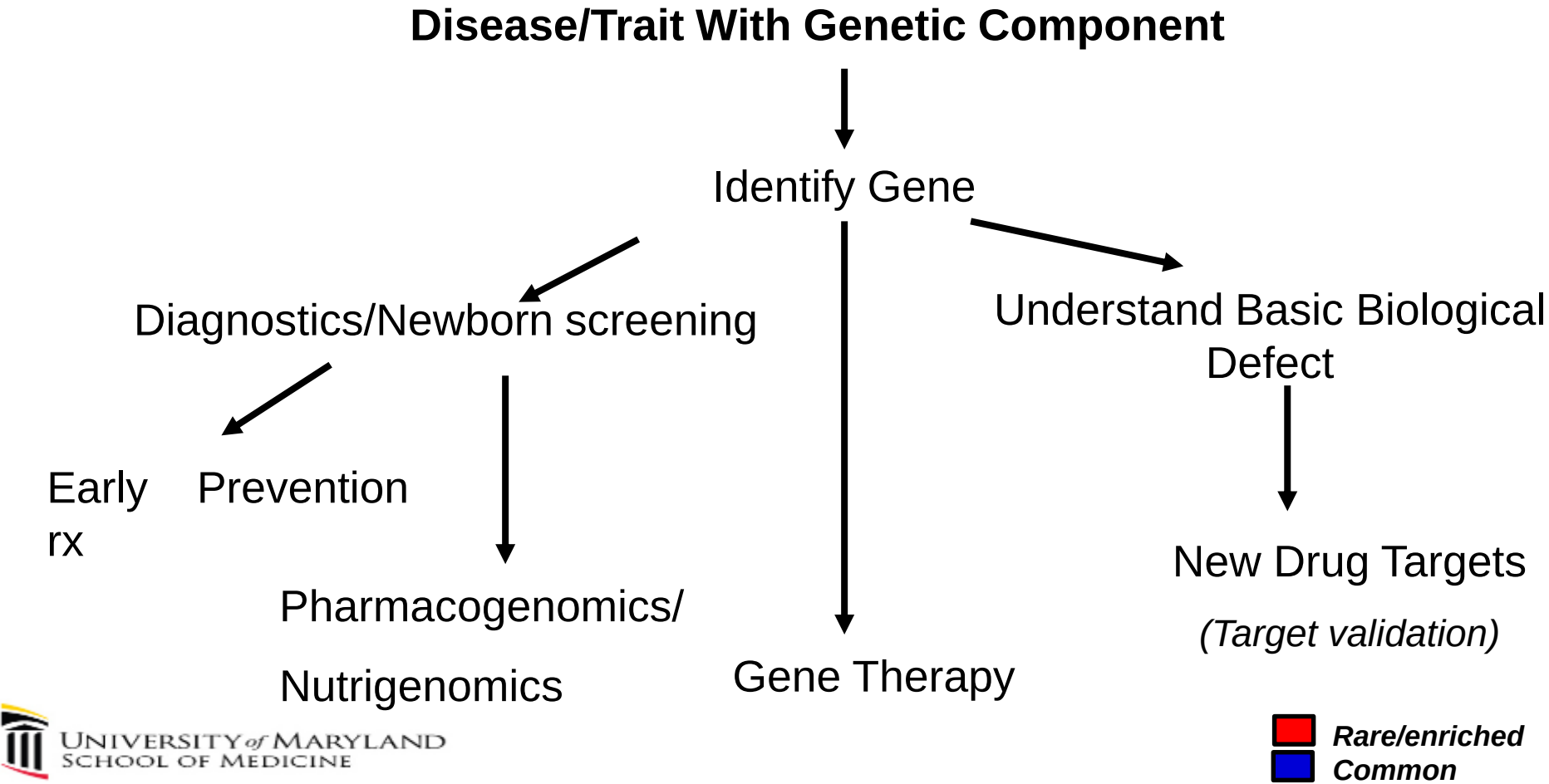
Expected minor allele homozygotes in n=6000

		Inbreeding Coefficient	
		0	0.035
MAF	0.5	1500	1553
	0.1	60	79
	0.05	15	25
	0.01	0.6	3

The Path to Personalized Medicine

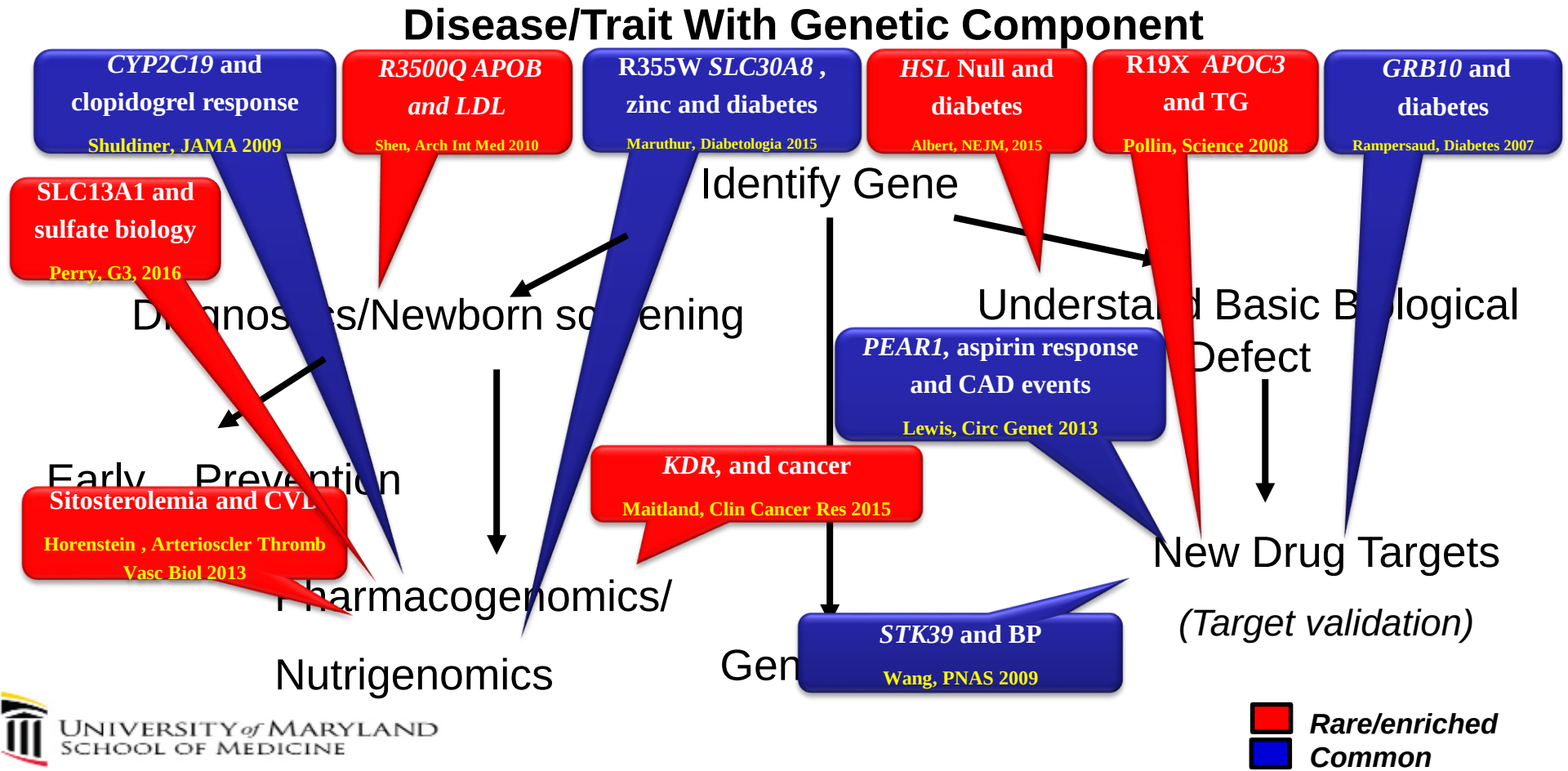


The Path to Personalized Medicine



Rare/enriched
Common

The Path to Personalized Medicine



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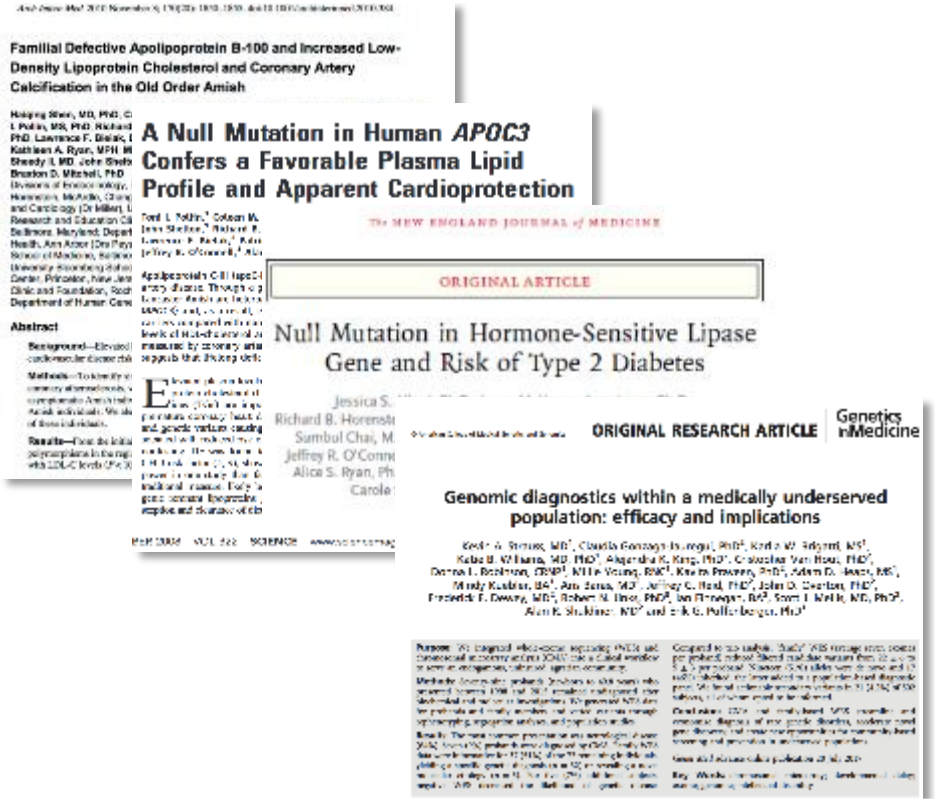
Some Cool Findings in the Amish:
Many drifted alleles that inform biology and precision medicine

- ~1in 8 Amish carry R3527Q *APOB*, a cause of autosomal dominant familial hypercholesterolemia (Shen et al. Arch Int Med 2010)
- ~ 1 in 25 Amish carry R19X *APOC3* and have low triglycerides levels and are protected from CAD (Pollin et al. Science 2008)
- ~ 1 in 40 Amish carry T224M *KCNQ1*, which is highly associated with longer QT interval, a risk factor for syncope and sudden death

Novel genes for monogenic diseases that inform biology and therapeutic development (Strauss, Genetics in Medicine 2017)

- ~ 1 in 20 Amish carry a 19 bp frame-shift mutation in *LIPE* that increases risk for T2D by 2-fold and causes partial lipodystrophy in homozygotes (Albert et al. NEJM 2014)



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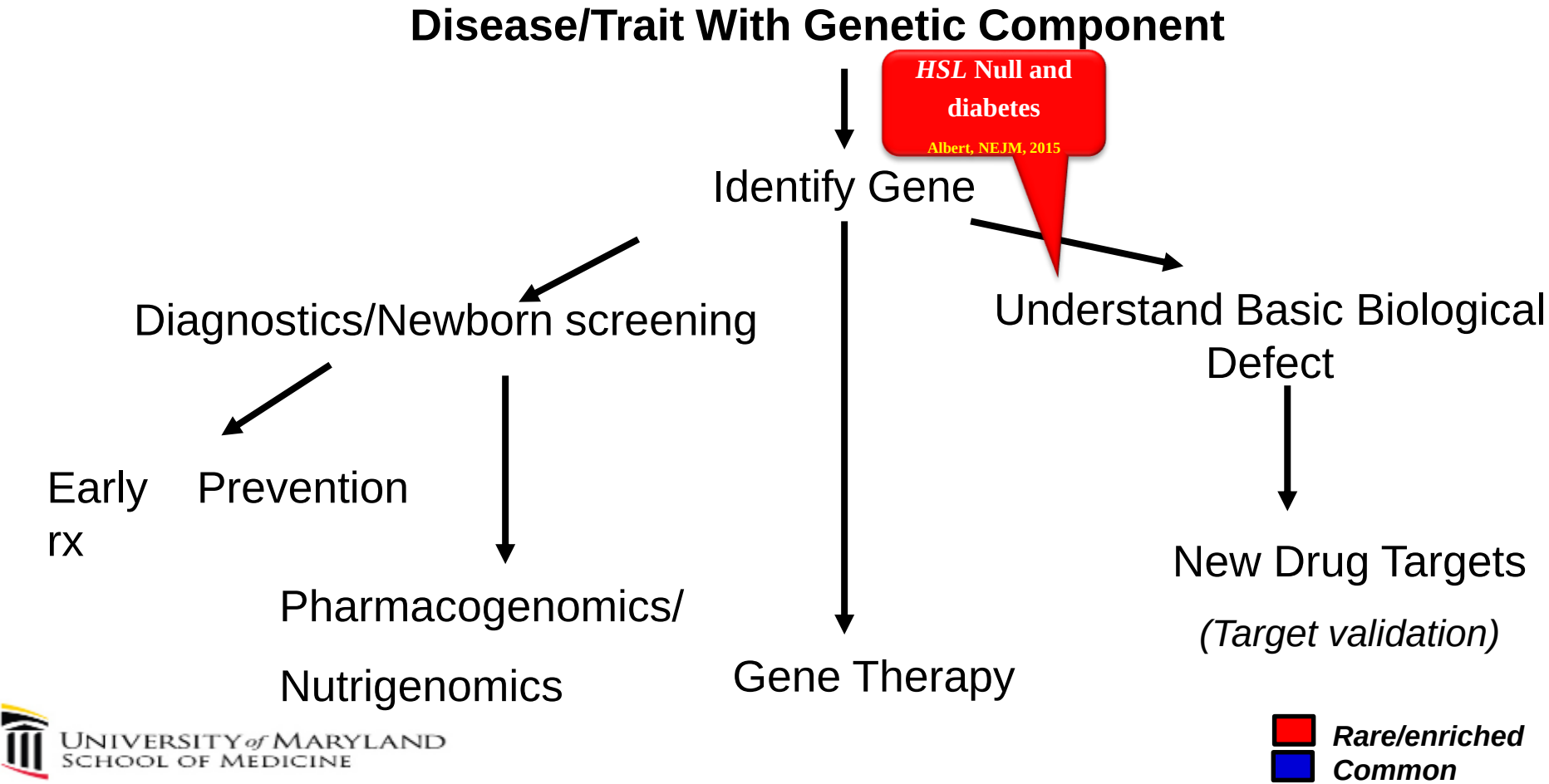


Rare/enriched
Common

The NEW ENGLAND JOURNAL of MEDICINE

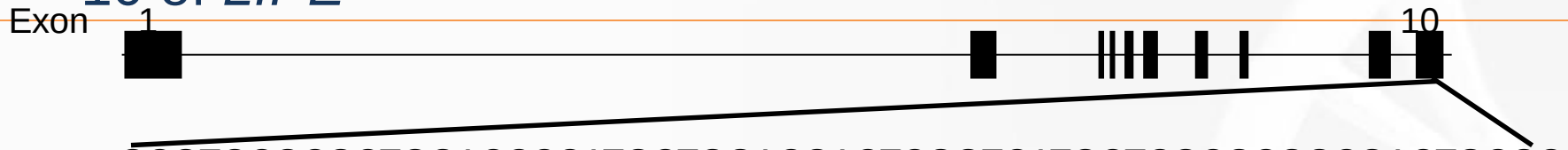
ORIGINAL ARTICLE

Null Mutation in Hormone-Sensitive Lipase Gene and Risk of Type 2 Diabetes

Jessica S. Albert, Ph.D., Laura M. Yerges-Armstrong, Ph.D., Richard B. Horenstein, M.D., Toni I. Pollin, Ph.D., Urmila T. Sreenivasan, M.S., Sumbul Chai, M.S., William S. Blaner, Ph.D., Soren Snitker, M.D., Ph.D., Jeffrey R. O'Connell, Ph.D., Da-Wei Gong, Ph.D., Richard J. Breyer III, M.D., Alice S. Ryan, Ph.D., John C. McLenithan, Ph.D., Alan R. Shuldiner, M.D., Carole Sztalryd, Ph.D., and Coleen M. Damcott, Ph.D.

June 2014

19 base pair deletion (p.V1068GfsX19) identified in exon 10 of *LIPE*



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TGCCTTACTTAAGTCGGGGGTGGCAAGGGGGCGGGGCGGGGGCCCGAAAGCTGAGA
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TGCACGCCACCGCTGCCTTTTGCTGCTGCTGCTGCGGCGACCGCCGCAGGGACGGG
GACTGGCCCTCCCTTGCAGGTCGGTTTGGTTTGTTGTAAATAAAAGTATTTAATTA

HSL

FABP4

Albert et al, NEJM, 2014

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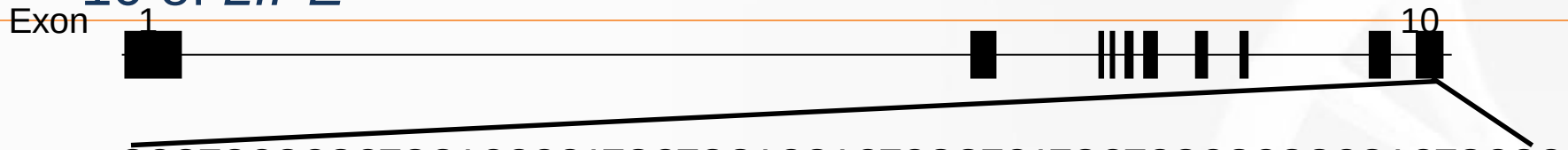

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GACTGGCCCTCCCTTGCAGGTCGGTTTGGTTTGTTGTAAATAAAAGTATTTAATTA

HSL

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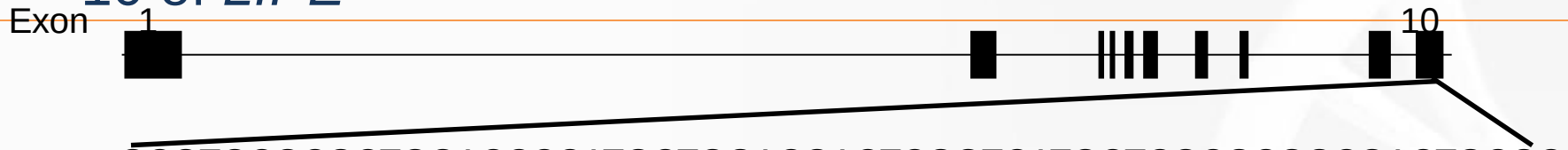

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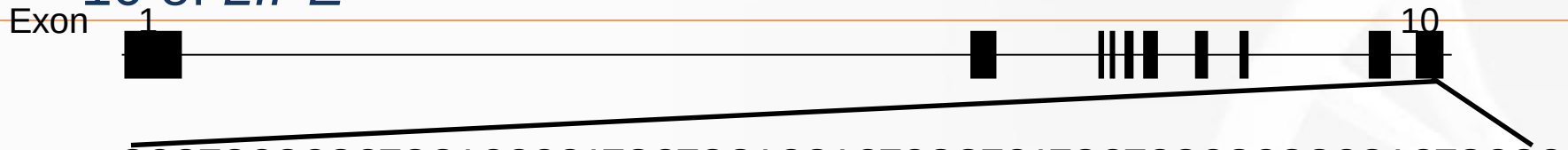
CCCTCGCCACGGGGAGGGGGACGCGCACACACACCGGTCACCGAGACGGCTGGACC
TGCACGCCACCGCTGCCTTTTGCTGCTGCTGCTGCGGCGACCGCCGCAGGGACGGG
GACTGGCCCTCCCTTGCAGGTCGGTTTGGTTTGTTGTAAATAAAAGTATTTAATTA

HSL ACALDPMLDDSVMLARRLRNLGQPVTLRVVEDLPHGFLTLAALCRETRQAAELCVERIR
LVLTPPAGAGPSGETGAAGVDGGCGGRH STOP

Albert et al, NEJM, 2014

19 base pair deletion (p.V1068GfsX19) identified in exon 10 of *LIPE*



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TGCACGCCACCGCTGCCTTTTGCTGCTGCTGCTGCGGCGACCGCCGCAGGGACGGG
GACTGGCCCTCCCTTGCAGGTCGGTTTGGTTTGTTGTAAATAAAAGTATTTAATTA

HSL ACALDPMLDDSVMLARRLRNLGQPVTLRVVEDLPHGFLTLAALCRETRQAAELCVERIR
LVLTPPAGAGPSGETGAAGVDGGCGGRH

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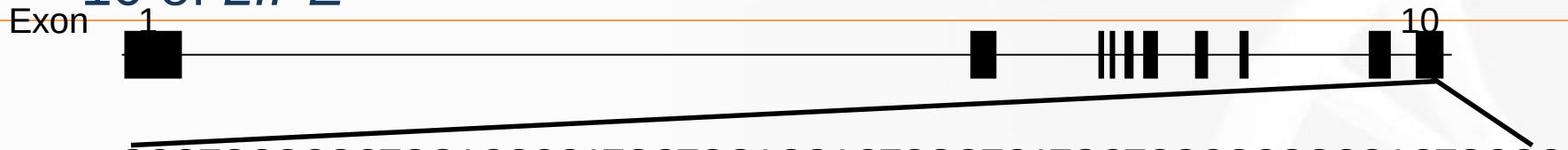

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TGCACGCCACCGCTGCCTTTTGCTGCTGCTGCTGCGGCGACCGCCGCAGGGACGGG
GACTGGCCCTCCCTTGCAGGTCGGTTTGGTTTGTTGTAAATAAAAGTATTTAATTA

HSL ACALDPMLDDSVMLARRLRNLGQPVTLRVVEDLPHGFLTLAALCRETRQAAELCVERIR
LVLTPPAGAGPSGETGAAGVDGGCGGRH

GDTKSLLFPSAPASVMNAFRAGRKGTRAVPYLSRGWQGGGAGARKLRPSPRGGGRAHTPVT
ETAGPARHRCLLLLLLRRPPQGRGLALPCRSVWFVVNKSI

FABP4

Albert et al, NEJM, 2014

19 base pair deletion (p.V1068GfsX19) identified in exon 10 of *LIPE*

GCGTGCGCGCTGGACCCCATGCTGGACGACTCGGTCATGCTCGCGCGGCGACTGCGC
AACCTGGGCCAGCCGGTGACGCTGCGCGTGGTGGAGGACCTGCCGCACGGCTTCCT
GACCCTA[illegible]CGTGGAGC
GCATCCC[illegible]AGACGGGG
GCTG[illegible]GTTCCCATC
TGCGCCC[illegible]GCGGGCTG
TGCCTTA[illegible]AGCTGAGA
CCCTCGC[illegible]GGCTGGACC
TGCACGCCACCGCTGCCTTTTGCTGCTGCTGCTGCGGCGACCGCCGCAGGGACGGG
GACTGGCCCTCCCTTGCAGGTCGGTTTGGTTTGTTGTAAATAAAAGTATTTAATTA

Amish carrier frequency = 0.013
(4 homozygotes)
GHS carrier frequency 0.00073
(No homozygotes)

HSL ACALDPMLDDSVMLARRLRNLGQPVTLRVVEDLPHGFLTLAALCRETRQAAELCVERIR
LVLTPPAGAGPSGETGAAGVDGGCGGRH

GDTKSLLFPSAPASVMNAFRAGRKGTRAVPYLSRGWQGGGAGARKLRPSPRGGGRAHTPVT
ETAGPARHRCLLLLLLRRPPQGRGLALPCRSVWFVVNKSI

Albert et al, NEJM, 2014

HSL knockout mouse

General

- Non-obese
- Male infertility

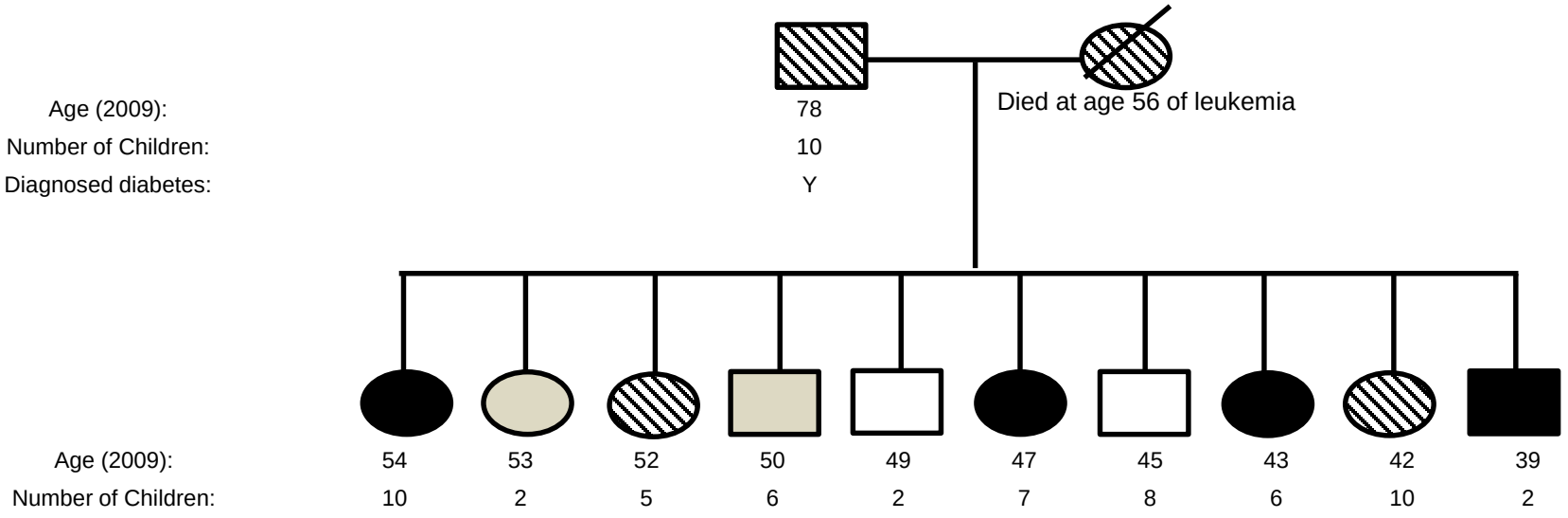
Adipose tissue

- Decreased lipolysis
- Increased DAG
- Decreased cholesterol esterase activity

Systemic

- Normoglycemic
- Normoinsulinemic
- Decreased TAG
- Increased HDL

Mating of heterozygous HSL Homo Sapiens



*not yet determined

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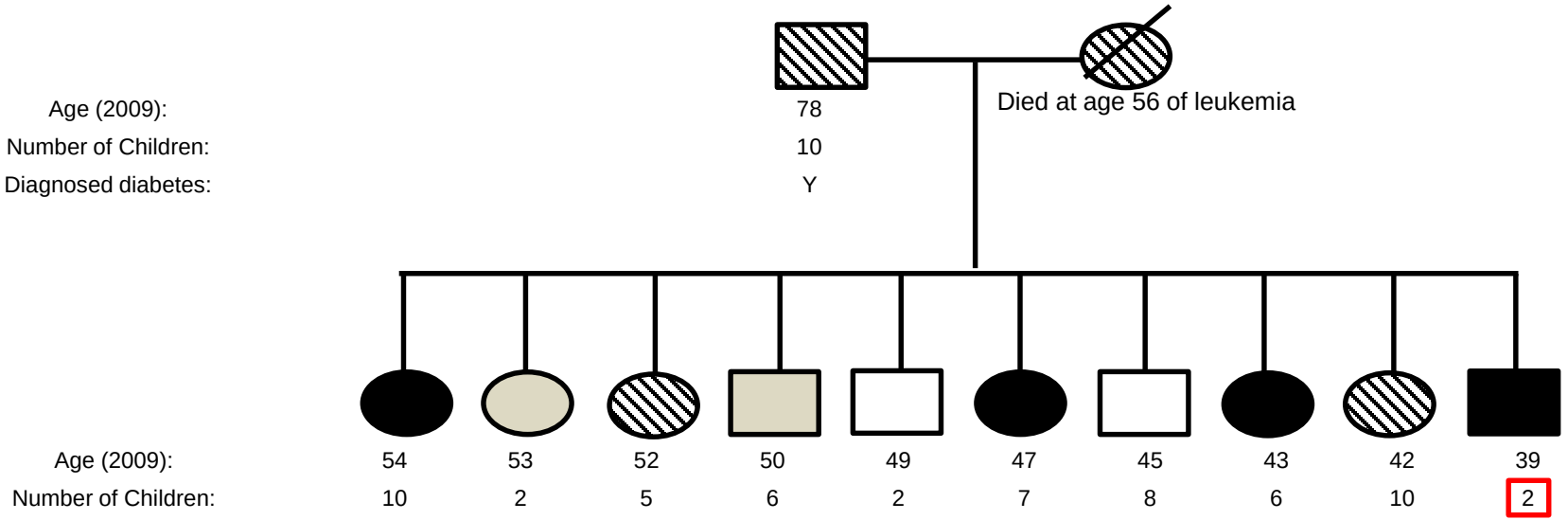
Albert et al, NEJM, 2014

Mating of heterozygous HSL Homo Sapiens



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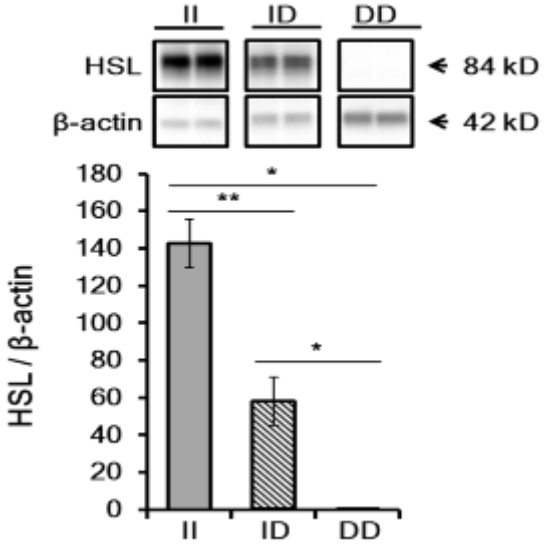
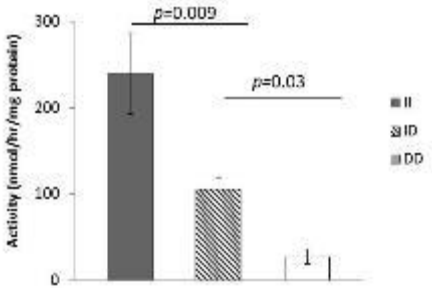
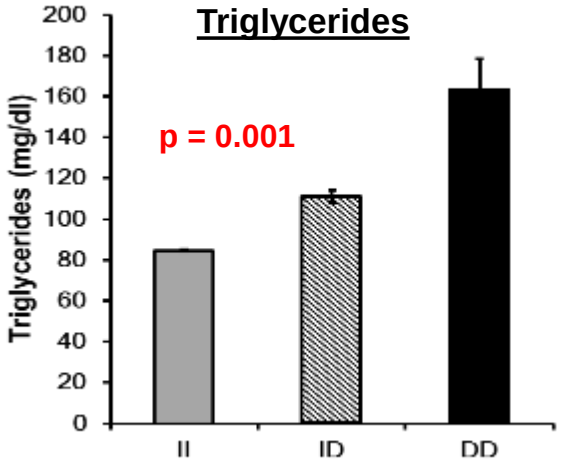
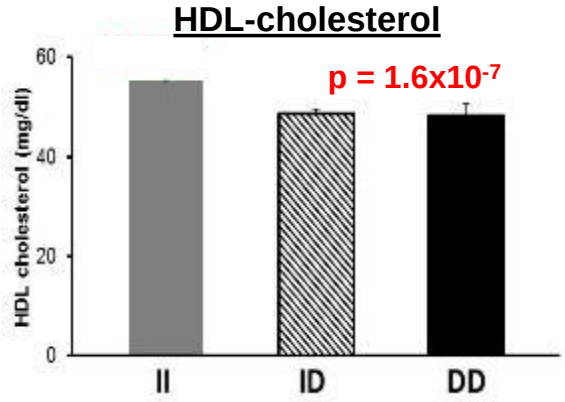
Albert et al, NEJM, 2014

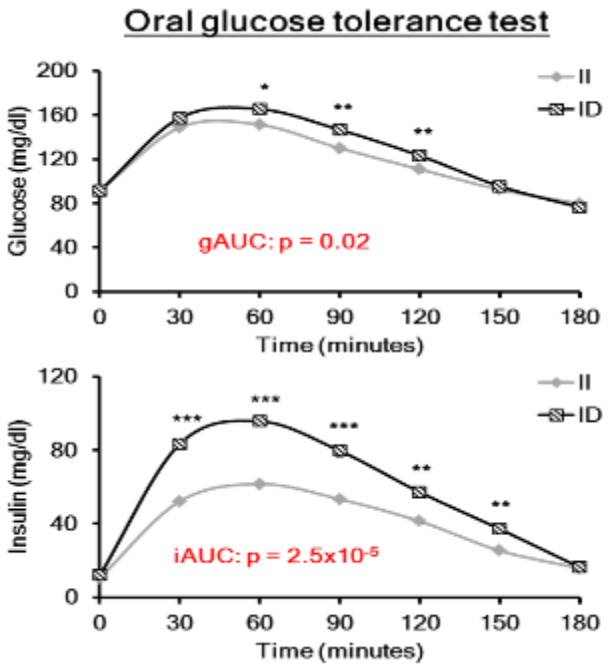
p.V1068GfsX19 HSL is a Null Mutation





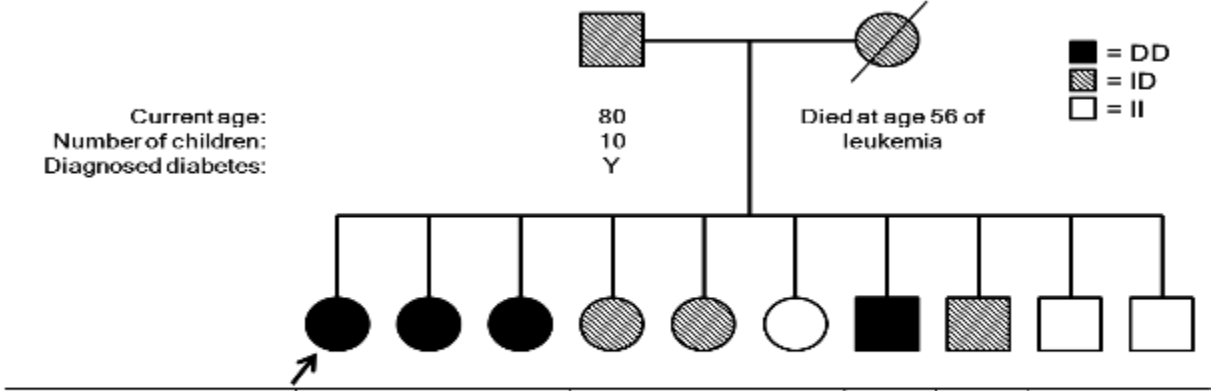






OR for DM = 2.0; p=0.02

Albert et al, NEJM, 2014

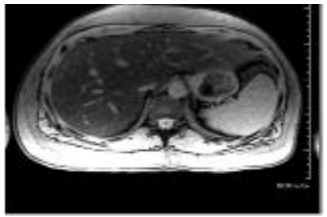
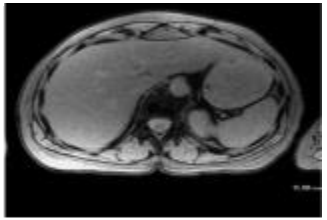
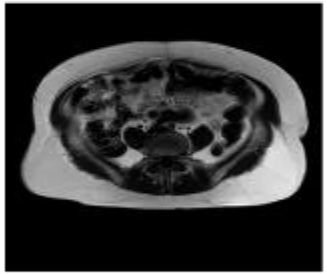
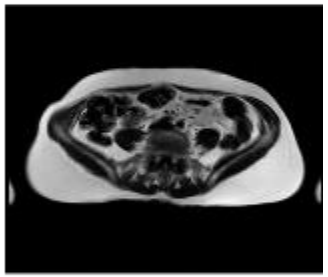
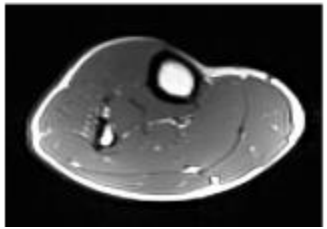
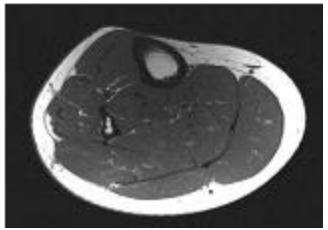


Subject number	1	2	3	4	5	6	7	8	9	10
Current age	46	49	56	44	53	55	42	51	47	52
BMI (kg/m^2)	27	28	27	31	23	23	29	22	24	29
Body Fat (%)	31.3	33.2	33.6	40.8	36.8	36.3	21.1	13.4	16.2	30.6
VAT (cm^2)	82.7	-	89	74.6	76.6	77.3	64.8	-	43.5	53.4
Abdominal SAT (cm^2)	276	-	318	316	205	212	193	-	79.9	222
Calf SAT (cm^2)	14.7	-	7.7	33.6	22.6	21.5	8.6	-	13.8	23.4
Abdominal SAT:Calf SAT	18.8	-	41.4	9.4	9.1	9.9	22.3	-	5.8	9.5
Liver Fat (%)	9.4	-	25.3	3.7	2.8	2.8	3.5	-	2.4	1.7
Adiponectin (µg/ml)	4.3	-	3.6	10.9	28	17.5	4.7	22.4	10.5	17.9
Leptin (ng/ml)	4.6	4.8	9.2	18.9	6.3	9	1.8	0.6	0.8	4.6
Fasting triglycerides (mg/dl)	148	152	256	81	140	109	193	53	73	146
HDL Cholesterol (mg/dl)	52	53	40	53	69	70	46	65	70	70
Fasting insulin (µU/ml)	7.9	20.3	15	7.6	2.6	9.1	5.6	3.3	4.6	-
Fasting glucose (mg/dl)	98	125	256	102	84	86	202	90	93	85
HOMA-IR	1.9	6.3	9.5	1.9	0.5	1.9	2.8	0.7	1.1	-
2-hr OGTT glucose (mg/dl)	204	-	-	140	119	101	470	112	150	107
Diagnosed diabetes (Age)	Y (46)	Y (46)	Y (48)	IGT	N	N	Y (40)	N	N	N
Number of offspring:	6	7	10	10	5	2	2	2	8	6

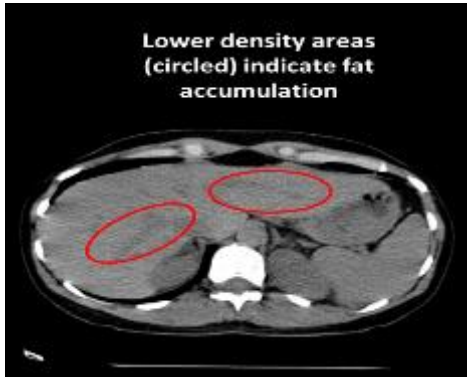
Albert et al, NEJM, 2014

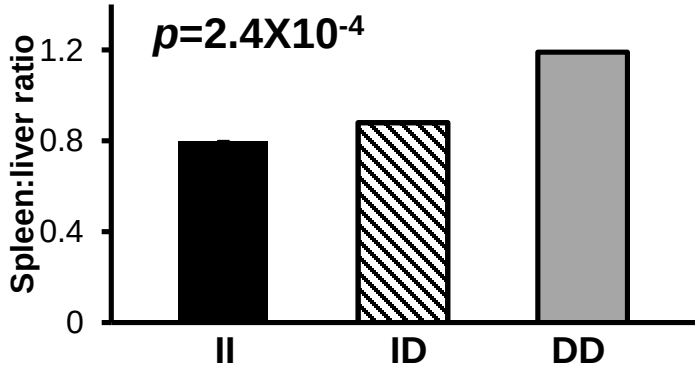
Increased liver and visceral fat; decreased LE fat in DD homozygotes

MRI

	DD Age 56 BMI 27 kg/m²	II Age 55 BMI 23 kg/m²
Liver (25.3% vs 2.8% fat)		
L4-L5/visceral fat (89.0 cm² vs. 77.3 cm)		
Calf 7.7 cm² vs 21.5 cm²		

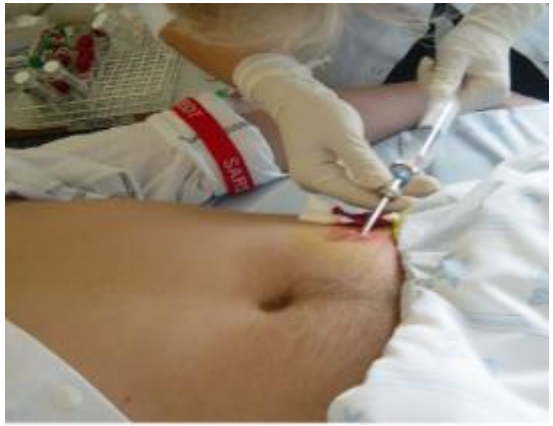
CT



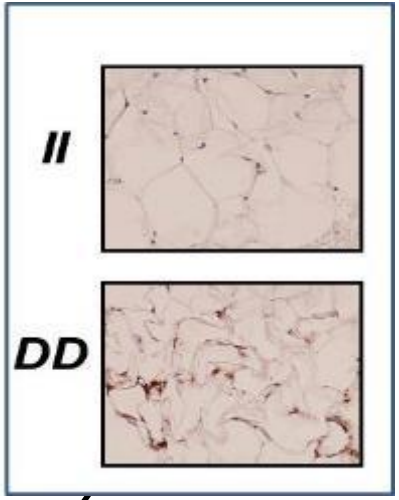


Albert et al, NEJM, 2014

Unexpected effect of HSL deficiency on adipocyte function



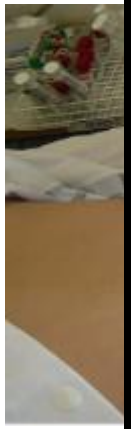
Liberase



- ↑ WAT cytokine release
- ↑ Infiltration by macrophages
- ↓ Expression of PPARγ- regluated genes
- ↓ Lipolysis
- ↓ Fat cell size
- ↓ Adipocyte insulin sensitivity

Albert et al, NEJM, 2014

Unexpected effect of HSL deficiency on adipocyte function



Implications:

In addition to its metabolic function, HSL may have an endocrine function to generate endogenous ligands for PPARγ

> ***Opportunity to identify endogenous ligand(s) for PPARγ as next diabetes therapeutic***

HSL KO (or deficient) humans with diabetes should respond well to PPARγ agonists (thiazolidinediones)

HSL activators as therapeutic to decrease TG and increase insulin sensitivity and glucose tolerance in patients with diabetes

cell
te

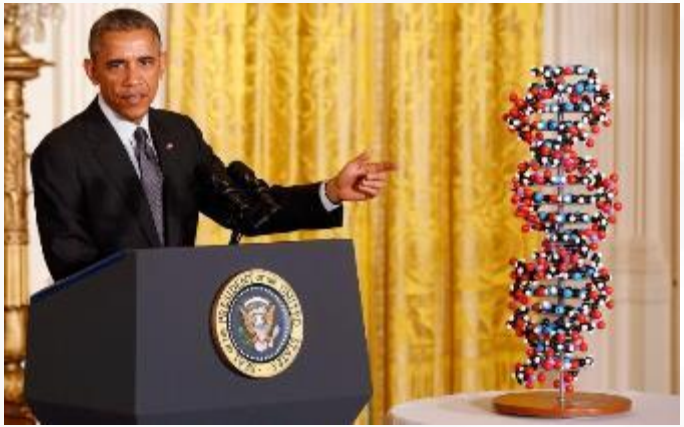
Albert et al, NEJM, 2014

Building the World's Largest Founder Population Collection for Discovery of Novel Disease-associated Genetic Variants:
Discovery Research Investigating Founder Population Traits (DRIFT) Goals

- Catalog population-specific allelic architecture
- Understand the biological and functional consequences of specific mutations identified
  - Genotype – Phenotype associations (especially of rare LoF/GoF mutations enriched in a given population
  - Replicate/extension in larger general population
  - "Genotype-first" call back studies
- Share and establish best practice approaches to relieve disease burden in these populations

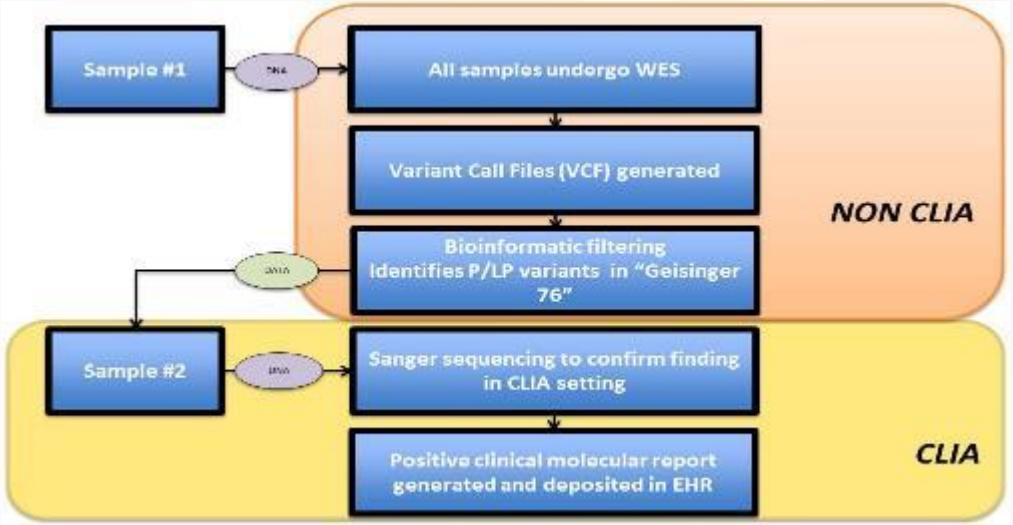
The Future of Precision Medicine is Here Today

The GHS Genome-First Return of Results Program



Geisinger GenomeFirst Program

- Informed consent specifies intent to return results that are medically actionable after CLIA confirmation
- Geisinger will NOT return results that are NOT medically actionable
- Geisinger experts will decide what to return
  - Geisinger “76” (56 ACMG + 20) genes causative of 27 diseases that are medically actionable
    - e.g., hereditary breast and ovarian cancer; Lynch syndrome; familial hypercholesterolemia; hypertrophic cardiomyopathy



Initial analyses indicate that ~3.5% of study participants will test positive for an actionable variant

Geisinger GenomeFirst Program

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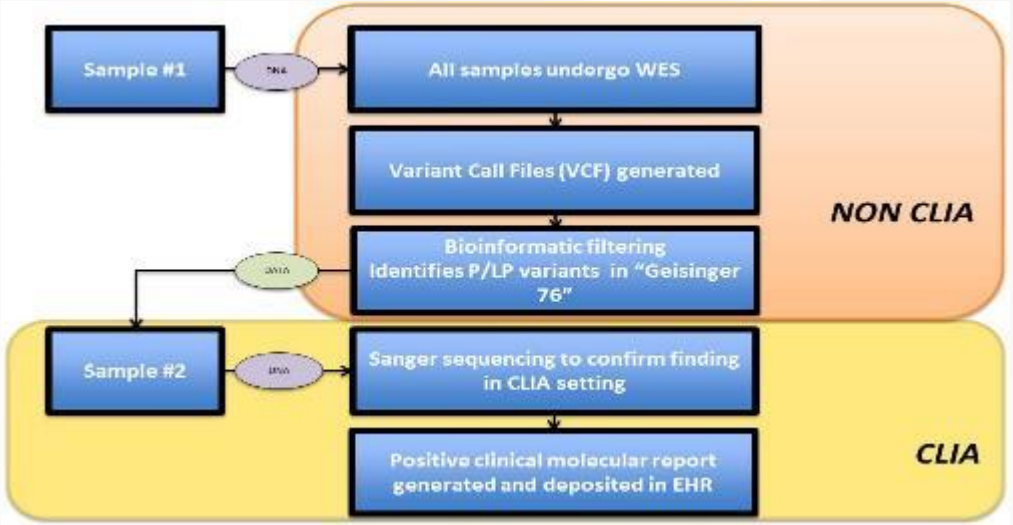


Geisinger 76: 1 in 25 Patients Have an Actionable Result

GENOMIC CONDITION	Number or patients diagnosed	CLINICAL RISK	DISEASE-ALTERING INTERVENTION
Familial Hypercholesterolemia (FH)	1 in 250	Early-onset Coronary Artery Disease and Stroke	Targeted screening and aggressive medical management
Hereditary Breast and Ovarian Cancer Syndrome	1 in 400	Early-onset Breast, Ovarian, and Prostate Cancers	Targeted screening with prophylactic medical and surgical intervention
Lynch Syndrome	1 in 440	Early-onset Colon and Uterine Cancers	Targeted screening and management of pre-cancerous changes
TOTAL	**> 1 in 100**	**Multiple Cancers and Cardiovascular Diseases**	**Life-saving screening and intervention before development of disease**

Other conditions: cardiomyopathy, long QT syndrome, malignant hyperthermia, arrhythmogenic right ventricular cardiomyopathy, MEN2, tuberous sclerosis, hereditary pheochromocytomas and paragangliomas

Barbara Barnes' MyCode Story

- 57 Year old grandmother bringing up three grandchildren ages 3, 5, and 14
- Found to have a pathogenic *BRCA1* mutation
  - "Okay, so what do we do next? I have 15 more years to go until they're raised."
- Genetic counseling and workup
  - Negative mammogram
  - Elected to have preventive bilateral salpingo-oophorectomy
  - Stage 1 cancer found in one fallopian tube
  - Completing chemotherapy with expected excellent outcome
  - Daughter tested for *BRCA1*

Kim Mummert's MyCode Story

- 66 year old GHS employee
- Tested positive for a Lynch Syndrome mutation
- Obtained genetic counseling
  - More frequent colonoscopy
  - Two children in their 20's will be screened

RESEARCH ARTICLE SUMMARY

Science
AAAS

HUMAN GENETICS

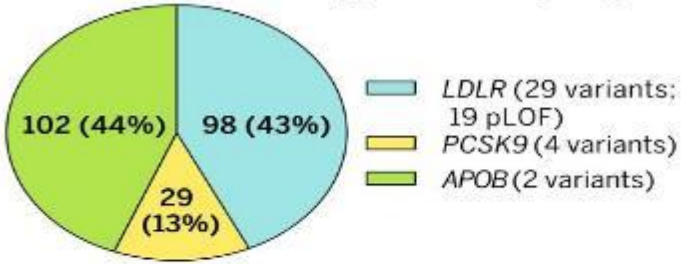
Genetic identification of familial hypercholesterolemia within a single U.S. health care system

Noura S. Abul-Husn, Kandamurugu Manickam, Laney K. Jones, Eric A. Wright, Dustin N. Hartzel, Claudia Gonzaga-Jauregui, Colm O'Dushlaine, Joseph B. Leader, H. Lester Kirchner, D'Andra M. Lindbuchler, Marci L. Barr, Monica A. Giovanni, Marylyn D. Ritchie, John D. Overton, Jeffrey G. Reid, Raghu P. R. Metpally, Amr H. Wardeh, Ingrid B. Borecki, George D. Yancopoulos, Aris Baras, Alan R. Shuldiner, Omri Gottesman, David H. Ledbetter, David J. Carey, Frederick E. Dewey, Michael F. Murray*

Prevalence and Clinical Impact of FH Variants in DiscovEHR

A

Distribution of 229 heterozygous carriers by FH gene

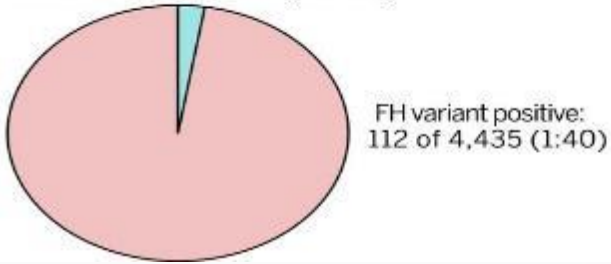


B

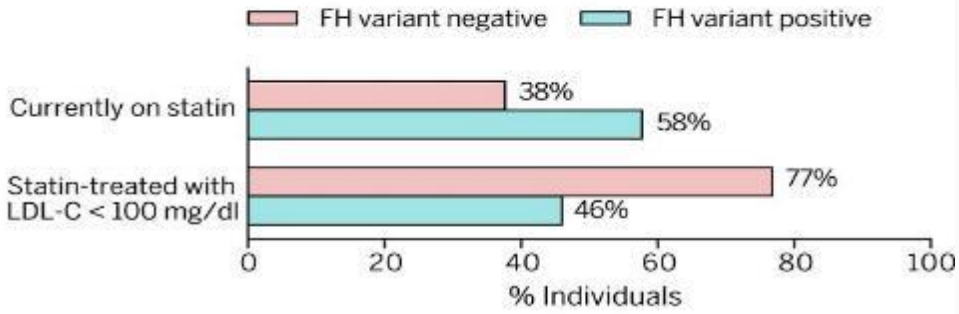
Population characteristics	FH variant positive/total	Estimated prevalence
All DiscovEHR participants	229/50,726	1:222
Participants recruited from cardiac catheterization lab	57/6,747	1:118
Participants recruited from other sites	172/43,979	1:256

C

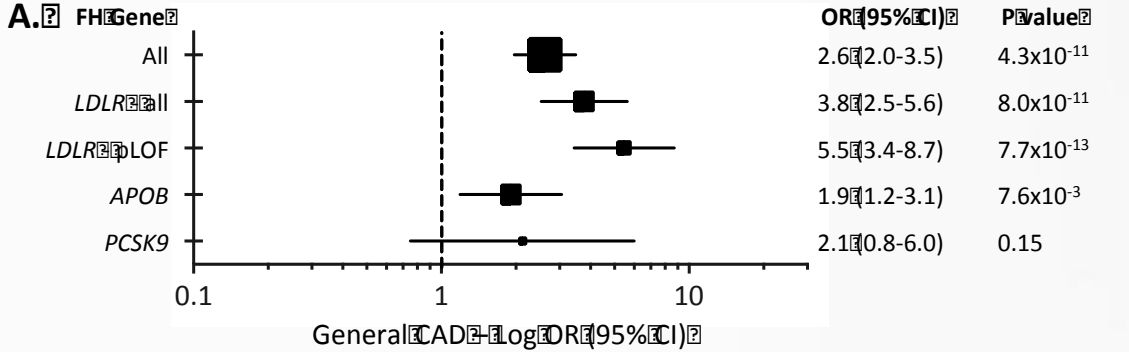
Participants with severe hypercholesterolemia (LDL-C > 190 mg/dl)
N = 4,435 of 42,696 individuals with LDL-C data available (10.4%)



D



Why GenomeFirst Is Important: Most patients with FH are not diagnosed and treated inadequately



- Only 35 (15.7%) of the 229 FH variant carriers had EHR evidence of a “Pure Hypercholesterolemia” diagnosis or at least one encounter at Lipid Clinic
- Criteria supporting a clinical diagnosis of FH were found using EHR data in only 55% of variant carriers
- Active statin use was identified in 58% and high-intensity statin use in 37% of carriers
- Only 46% of statin-treated carriers had a LDL cholesterol level below 100 mg/dl.
- Genomic screening can prompt the diagnosis of FH patients, the majority of whom are receiving inadequate lipid-lowering therapy

Abul-Husn et al, Science 2016

Summary and Conclusions

- The future of drug discovery and precision medicine will be fueled by human genomic discovery
- Genetic “experiments of nature” can inform therapeutic target discovery and provide insight into mechanism
- Return of medically actionable genetic results will require significant health care system resources to realize downstream health and economic benefits
- Partnerships between industry, academia and health care systems can accelerate genomic discovery and implementation of precision medicine

Acknowledgements – Regeneron and Collaborators

Thank you to the thousands of patients, volunteers, collaborators, investigators, and scientists who make this work possible

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Aris Economides
John Overton
Jeff Reid
Alan Shuldiner

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