Precision Health
Are we ready to use genomics to promote behavioral change?

Laura Jean Bierut, MD
Alumni Endowed Professor of Psychiatry

June 10th, 2025

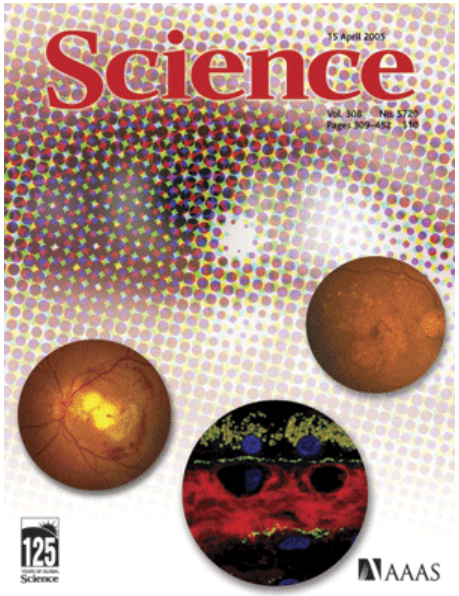
Washington University in St. Louis
School of Medicine

Precision Prevention
Table of Contents

Chapter 1

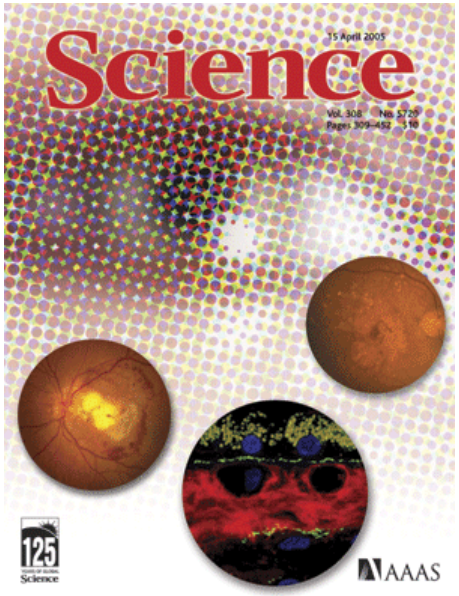
The new genetic world

2005 Time Zero – New Era in Genetic Studies



April 15, 2005

2005 Time Zero – New Era in Genetic Studies



GENETICS

Was the Human Genome Project Worth the Effort?

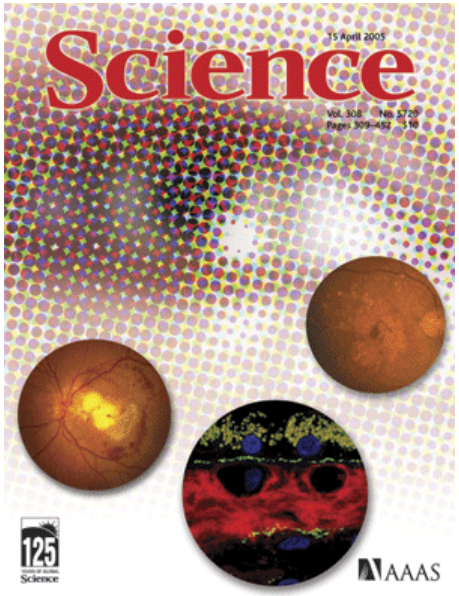
Stephen P. Daiger

One of the promises of the Human Genome Project was that it would

fected individuals. AMD afflicts more than 10 million Americans and is the leading

April 15, 2005

2005 Time Zero – New Era in Genetic Studies



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GENETICS

Was the Human Genome Project Worth the Effort?

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...ividuals. AMD afflicts more than ...n Americans and is the leading

Complement Factor H Polymorphism and Age-Related Macular Degeneration

Albert O. Edwards,[1*†] Robert Ritter III,[1] Kenn... Alisa Manning,[3] Carolien Panhuysen,[3,6] Lindsay ...

Age-related macular degeneration (AMD) is a common, la... plex trait with multiple risk factors. Concentrating on a ... locus for AMD on 1q25-31, the *ARMD1* locus, we teste... polymorphisms for association with AMD in two indepe... populations. Significant association ($P = 4.95 \times 10^{-7}$...

REPORTS

Complement Factor H Variant Increases the Risk of Age-Related Macular Degeneration

Jonathan L. Haines,[1] Michael A. Hauser,[2] Silke Schmidt,[2] William K. Scott,[2] Lana M. Olson,[1] Paul Gallins,[2] Kylee L. Spencer,[1] Shu Ying Kwan,[2] Maher Noureddine,[2] John R. Gilbert,[2] Nathalie Schnetz-Boutaud,[1] Anita Agarwal,[3] Eri... Margaret A. Pericak-Vance[2*]

Age-related macular degeneration (AMD) is a leading cause... ment and blindness in the elderly whose etiology remains ... Previous studies identified chromosome 1q32 as harboring ... locus for AMD. We used single-nucleotide polymorphisms ...

Complement Factor H Polymorphism in Age-Related Macular Degeneration

Robert J. Klein,[1] Caroline Zeiss,[2*] Emily Y. Chew,[3*] Jen-Yue Tsai,[4*] Richard S. Sackler,[1] Chad Haynes,[1] Alice K. Henning,[5] John Paul SanGiovanni,[3] Shrikant M. Mane,[6] Susan T. Mayne,[7] Michael B. Bracken,[7] Frederick L. Ferris,[3] Jurg Ott,[1] Colin Barnstable,[2] Josephine Hoh[7†]

Age-related macular degeneration (AMD) is a major cause of blindness in the elderly. We report a genome-wide screen of 96 cases and 50 controls for

NHGRI-EBI Catalog

Genome Wide Significant Associations

December 2005

NHGRI-EBI Catalog

Genome Wide Significant Associations

December 2005

NHGRI-EBI Catalog

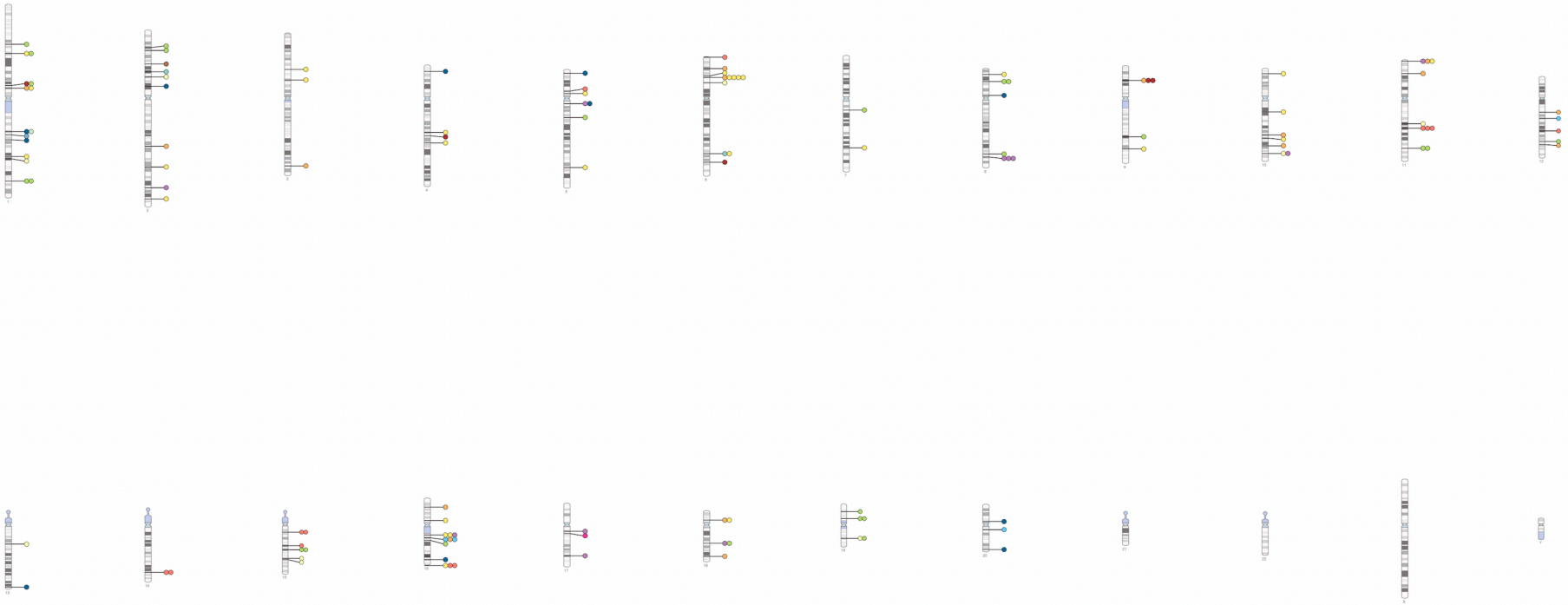
Genome Wide Significant Associations

December 2006

NHGRI-EBI Catalog

Genome Wide Significant Associations

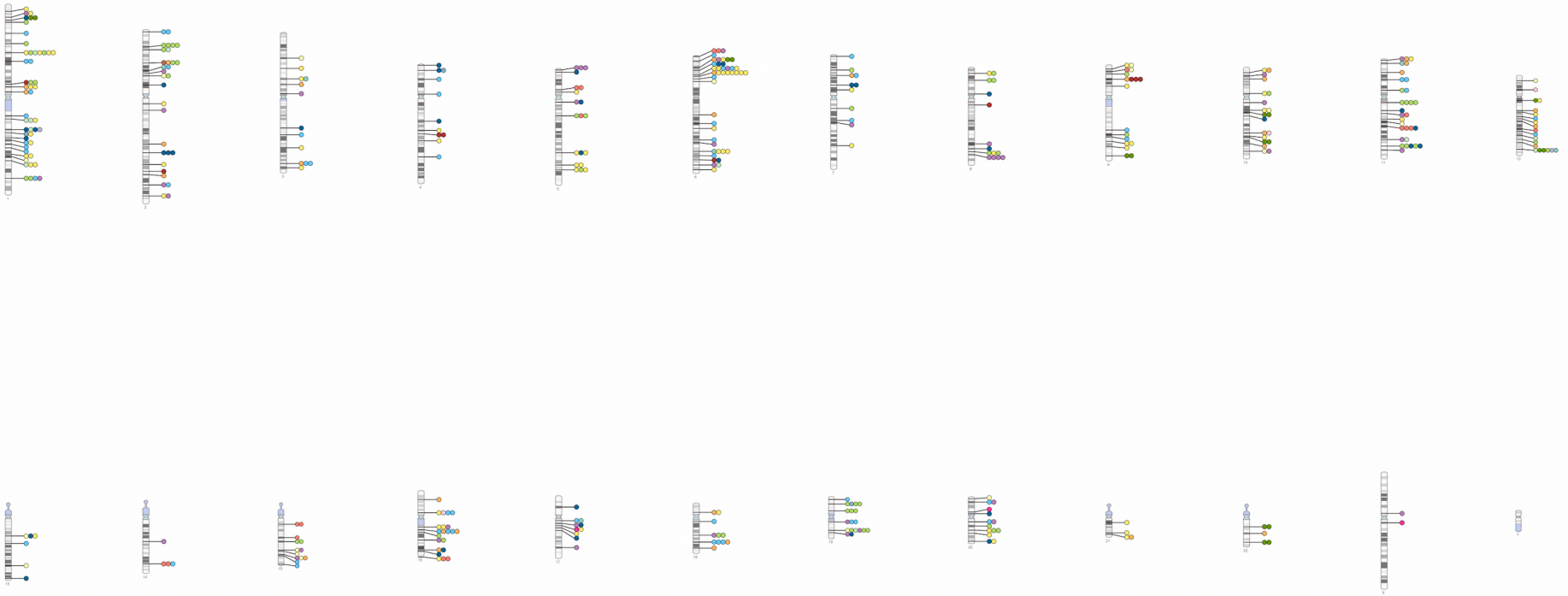
December 2007



NHGRI-EBI Catalog

Genome Wide Significant Associations

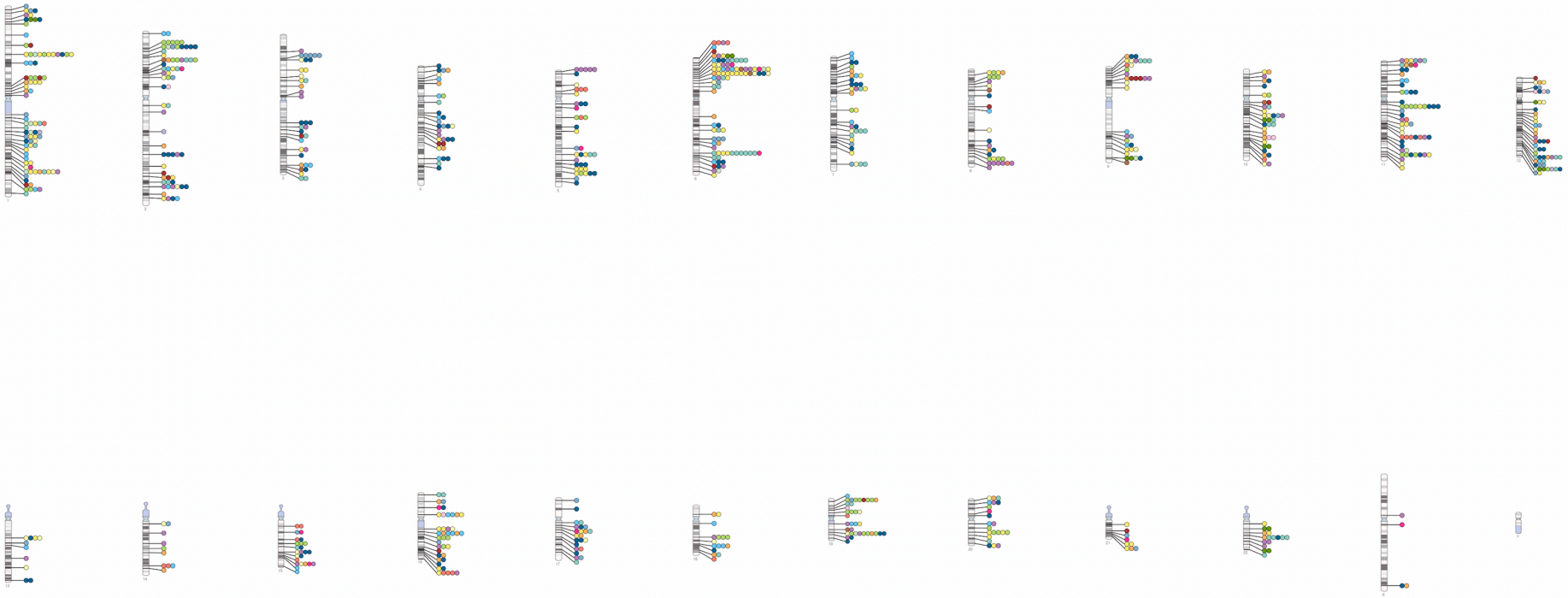
December 2008



NHGRI-EBI Catalog

Genome Wide Significant Associations

December 2009



NHGRI-EBI Catalog

Genome Wide Significant Associations

December 2010

NHGRI-EBI Catalog

Genome Wide Significant Associations

December 2011

NHGRI-EBI Catalog

Genome Wide Significant Associations

December 2012

NHGRI-EBI Catalog

Genome Wide Significant Associations

December 2013

NHGRI-EBI Catalog

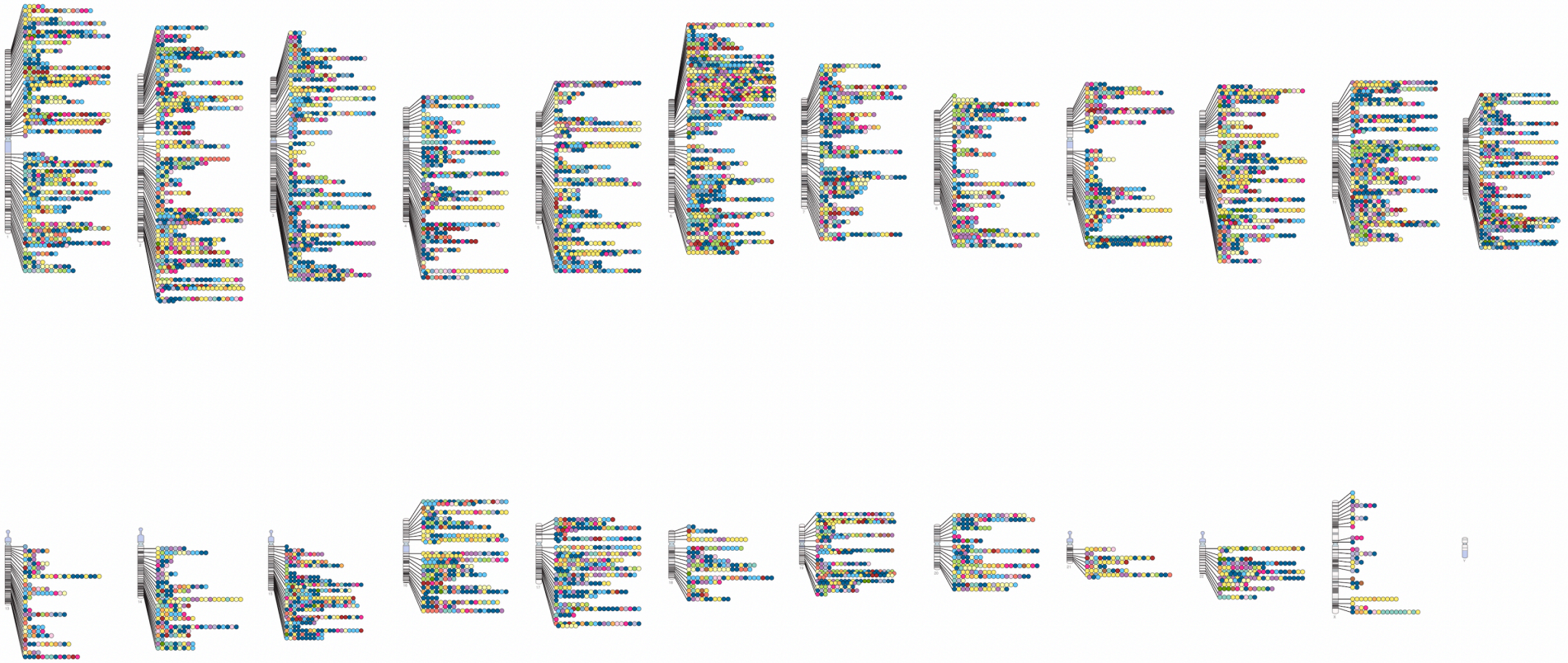
Genome Wide Significant Associations

December 2014

NHGRI-EBI Catalog

Genome Wide Significant Associations

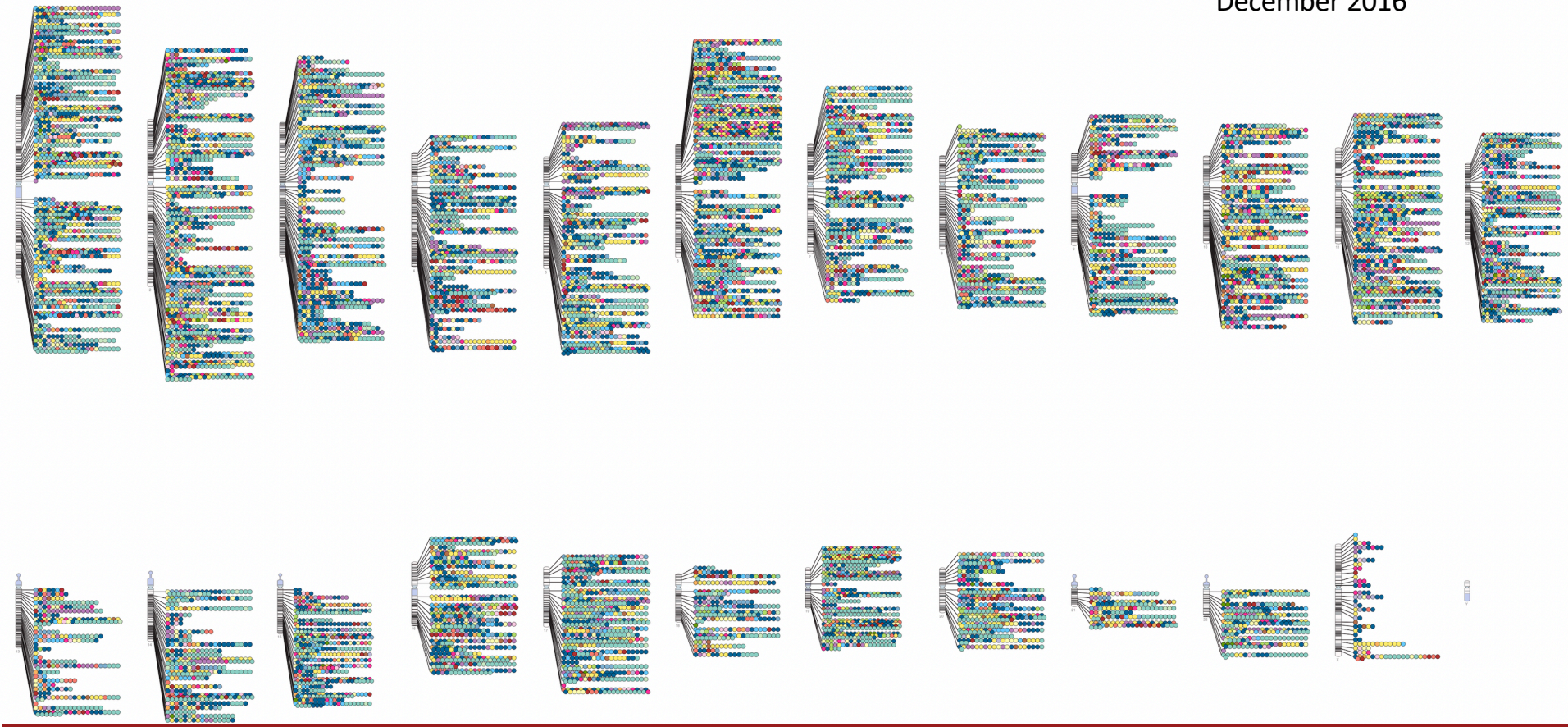
December 2015



NHGRI-EBI Catalog

Genome Wide Significant Associations

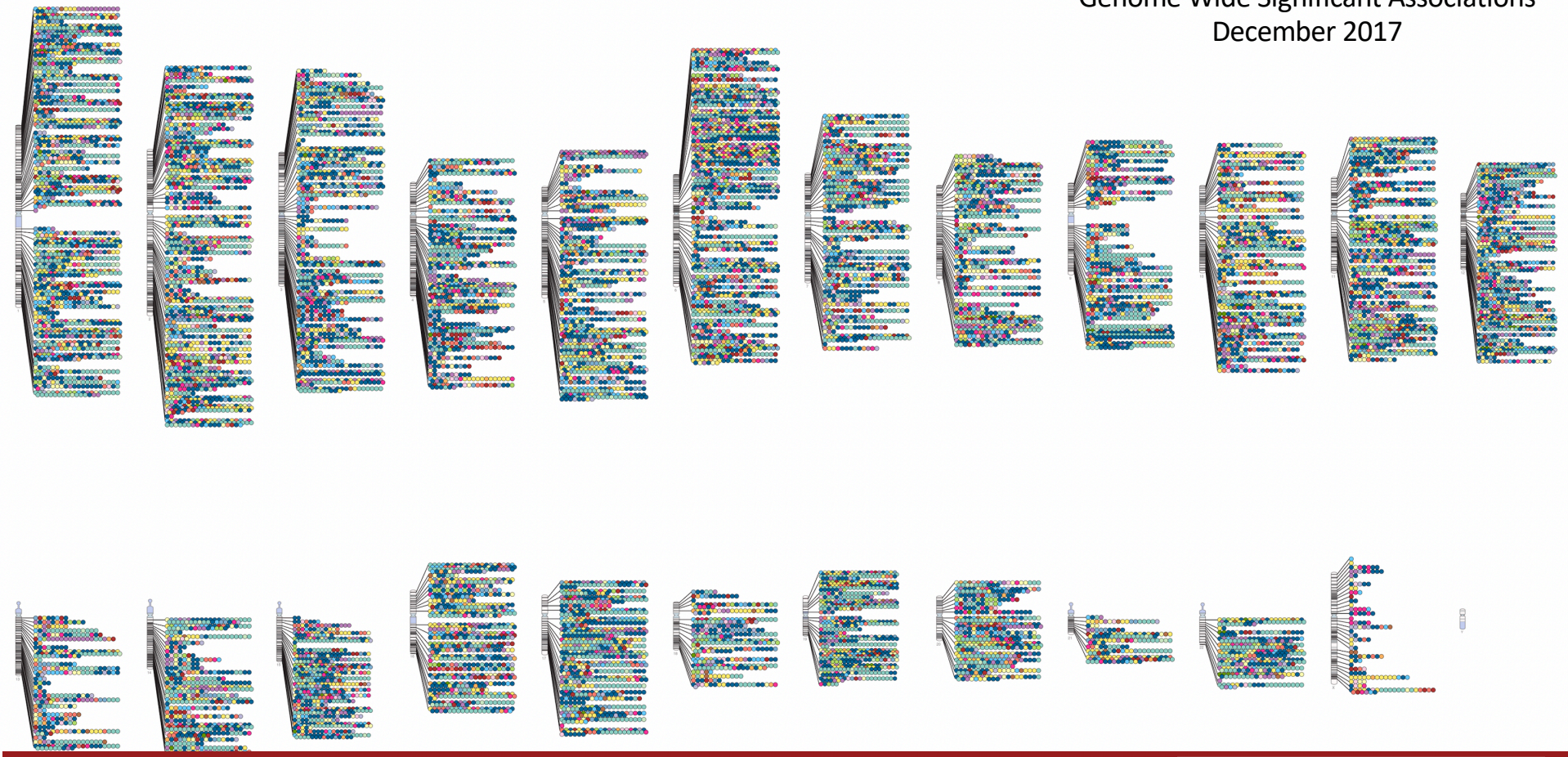
December 2016



NHGRI-EBI Catalog

Genome Wide Significant Associations

December 2017



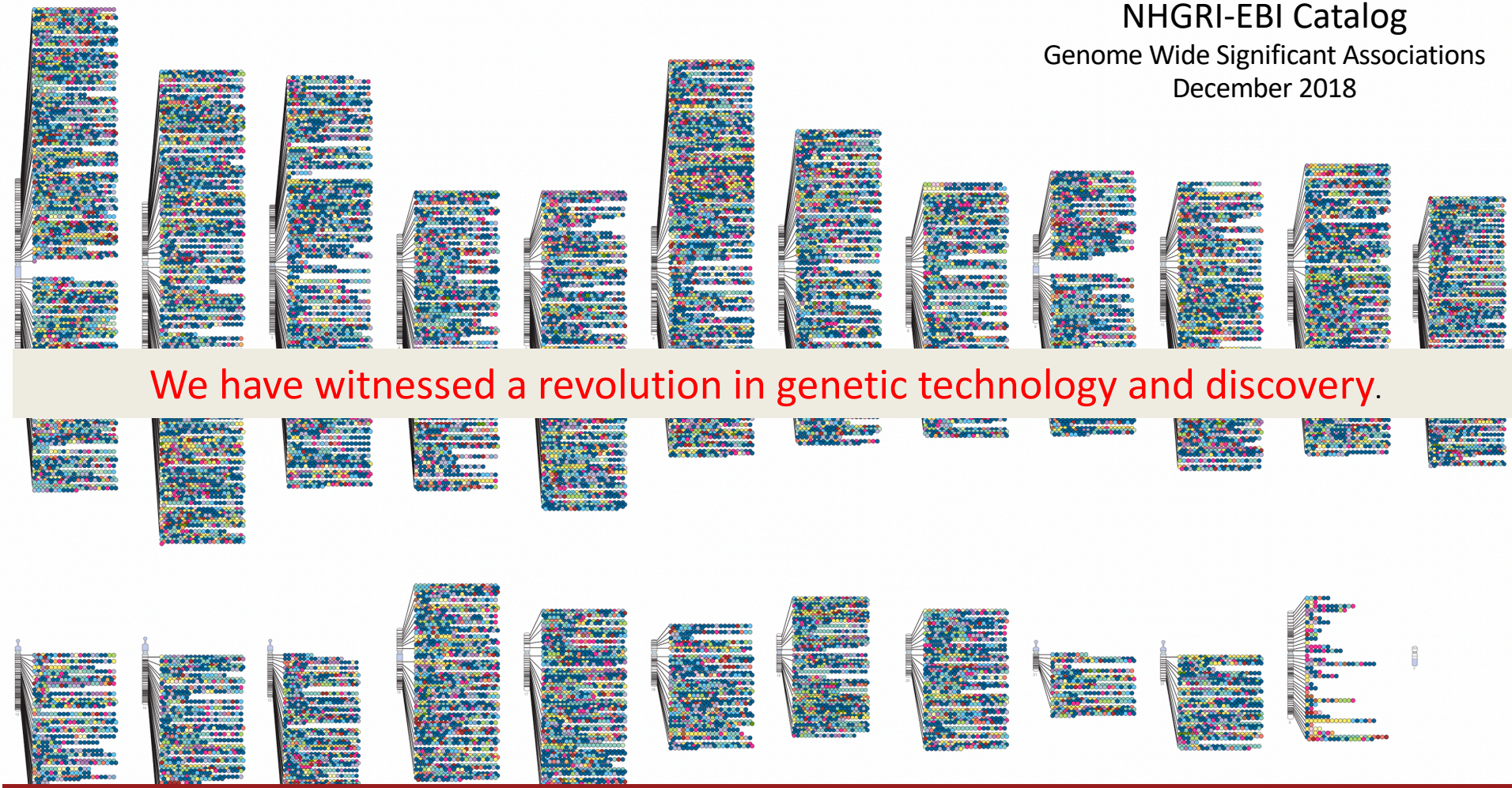
NHGRI-EBI Catalog

Genome Wide Significant Associations

December 2018

NHGRI-EBI Catalog

Genome Wide Significant Associations
December 2018



We have witnessed a revolution in genetic technology and discovery.

Chapter 2

Nicotine use disorder requires smoking initiation

Environmental and genetic factors influence each step in the transition to addiction

Genetic factors strongly influence the transition to nicotine use disorder

Chapter 3

Variation in genes for nicotinic acetylcholine receptors and nicotine metabolism are the strongest contributors to smoking behaviors.

Novel genes identified in a high-density genome wide association study for nicotine dependence

Laura Jean Bierut[1,*], Pamela A.F. Madden[1], Naomi Breslau[2], Eric O. Johnson[3], Dorothy Hatsukami[4], Ovide F. Pomerleau[5], Gary E. Swan[6], Joni Rutter[7], Sarah Bertelsen[1], Louis Fox[1], Douglas Fugman[8], Alison M. Goate[1], Anthony L. Hinrichs[1], Karel Konvicka[9], Nicholas G. Martin[10], Grant W. Montgomery[10], Nancy L. Saccone[1], Scott F. Saccone[1], Jen C. Wang[1], Gary A. Chase[11], John P. Rice[1] and Dennis G. Ballinger[9]

[1]Department of Psychiatry, Washington University
63110, USA, [2]Michigan State University, East Lans
Triangle Park, NC, USA, [4]University of Minnesota,
USA, [6]SRI International, Menlo Park, CA, USA, [7]N
University, Piscataway, NJ, USA, [9]Perlegen Scienc
Research, Herston QLD, Australia and [11]Penn Sta

Cholinergic nicotinic receptor genes implicated in a nicotine dependence association study targeting 348 candidate genes with 3713 SNPs

Scott F. Saccone[1,*,†], Anthony L. Hinrichs[1,†], Nancy L. Saccone[1], Gary A. Chase[3], Karel Konvicka[4], Pamela A.F. Madden[1], Naomi Breslau[5], Eric O. Johnson[6], Dorothy Hatsukami[7], Ovide Pomerleau[8], Gary E. Swan[9], Alison M. Goate[1,2], Joni Rutter[10], Sarah Bertelsen[1], Louis Fox[1], Douglas Fugman[11], Nicholas G. Martin[12], Grant W. Montgomery[12], Jen C. Wang[1], Dennis G. Ballinger[4], John P. Rice[1,2] and Laura Jean Bierut[1]

Human Molecular Genetics 2007

Molecular Psychiatry (2008) 13, 368–373

www.nature.com/mp

IMMEDIATE COMMUNICATION

α-5/α-3 nicotinic receptor subunit alleles increase risk for heavy smoking

W Berrettini[1,2,3], X Yuan[2,3], F Tozzi[2,3], K Song[2,3], C Francks[2,3], H Chilcoat[4], D Waterworth[2,3], P Muglia[2,3,5] and V Mooser[2,3]

[1]*Department of Psychiatry, University of Pennsylvania Schoo*
Discovery Medicine, GlaxoSmithKline, Upper Merion, PA, U
GlaxoSmithKline, Verona, Italy; [4]Worldwide Epidemiology, Gl
of Toronto, Toronto, ON, Canada

A variant associated with nicotine dependence, lung cancer and peripheral arterial disease

Thorgeir E. Thorgeirsson[1]*, Frank Geller[1]*, Patrick Sulem[1]*, Thorunn Rafnar[1]*, Anna Wiste[1,2], Kristinn P. Magnusson[1], Andrei Manolescu[1], Gudmar Thorleifsson[1], Hreinn Stefansson[1], Andres Ingason[1], Simon N. Stacey[1], Jon T. Bergthorsson[1], Steinunn Thorlacius[1], Julius Gudmundsson[1], Thorlakur Jonsson[1], Margret Jakobsdottir[1], Jona Saemundsdottir[1], Olof Olafsdottir[1], Larus J. Gudmundsson[1], Gyda Bjornsdottir[1], Kristleifur Kristjansson[1], Halla Skuladottir[3], Helgi J. Isaksson[4], Tomas Gudbjartsson[5], Gregory T. Jones[8], Thomas Mueller[9], Anders Gottsäter[10], Andrea Flex[11], Katja K. H. Aben[12,13], Femmie de Vegt[12], Peter F. A. Mulders[14], Dolores Isla[15], Maria J. Vidal[15], Laura Asin[16], Berta Saez[17], Laura Murillo[18], Thorsteinn Blondal[19], Halldor Kolbeinsson[6], Jon G. Stefansson[6], Ingunn Hansdottir[20], Valgerdur Runarsdottir[20], Roberto Pola[11,21], Bengt Lindblad[10], Andre M. van Rij[8], Benjamin Dieplinger[9], Meinhard Haltmayer[9], Jose I. Mayordomo[15,16,17], Lambertus A. Kiemeney[12,13,14], Stefan E. Matthiasson[22], Hogni Oskarsson[23], Thorarinn Tyrfingsson[20], Daniel F. Gudbjartsson[1], Jeffrey R. Gulcher[1], Steinn Jonsson[7], Unnur Thorsteinsdottir[1,22], Augustine Kong[1] & Kari Stefansson[1,22]

Nature, 2008

nature genetics

Sequence variants at *CHRNB3–CHRNA6* and *CYP2A6* affect smoking behavior

Thorgeirsson et al., 2010

Smoking is a common risk factor for many diseases[1]. We conducted genome-wide associati
number of cigarettes smoked per
($n = 31,266$) and smoking initiati
from the ENGAGE Consortium. I
selected SNPs with *in silico* replic
Genetics (TAG) and Glaxo Smith
cohorts ($n = 45,691$ smokers) an
third sample of European ancestr
genomic regions associated with C
previously identified SNPs at 15q
(effect size = 0.80 CPD, $P = 2.4 \times$
8p11, represented by rs4105144[
$P = 2.2 \times 10^{-12}$) and rs6474412-T
$P = 1.4 \times 10^{-8}$), respectively. Amo
associated loci are genes encodin
enzymes (*CYP2A6* and *CYP2B6*)
receptor subunits (*CHRNB3* and
been highlighted in previous stud
dependence[2–4]. Nominal associat
observed at both 8p11 (rs6474412[T], odds ratio (OR) = 1.09,

Genome-wide meta-analyses identify multiple loci associated with smoking behavior

TAG Consortium, 2010

The Tobacco and Genetics Con

Consistent but indirect evidence has
in smoking behavior[1,2]. We report n
smoking phenotypes within cohorts
Consortium ($n = 74,053$). We also p
Network of Genetic and Genomic E
and Oxford-GlaxoSmithKline (Ox-G
the 15 most significant regions ($n >$
three loci associated with number o
per day. The strongest association w
SNP in the nicotinic receptor gene
1.03, standard error (s.e.) = 0.053,
SNPs (rs1329650[G], $\beta = 0.367$, s.e

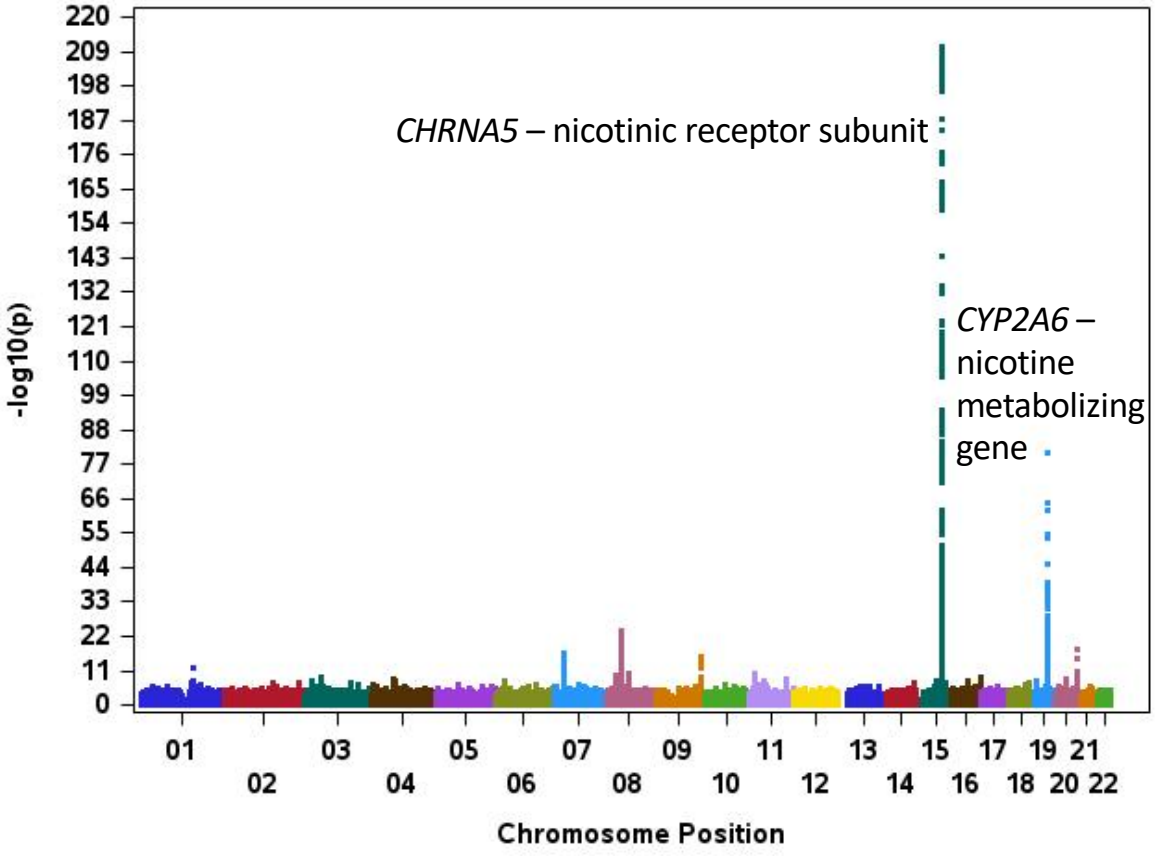
Meta-analysis and imputation refines the association of 15q25 with smoking quantity

Liu et al., 2010

Smoking is a leading global cause of disease and mortality[1]. We established the Oxford-GlaxoSmithKline study (Ox-GSK) to perform a genome-wide meta-analysis of SNP association with smoking-related behavioral traits. Our final data set included 41,150 individuals drawn from 20 disease, population and control cohorts. Our analysis confirmed an effect on smoking quantity at a locus on 15q25 ($P = 9.45 \times 10^{-19}$) that includes *CHRNA5*, *CHRNA3* and *CHRNB4*, three genes encoding neuronal nicotinic acetylcholine receptor subunits. We used data from the 1000 Genomes project to investigate the region using imputation, which allowed for analysis of virtually all common SNPs in the region and offered a fivefold increase in marker density over HapMap2 (ref. 2) located within the promoter region of *CHRNA5*. Conditional analysis also identified a secondary locus (rs6495308) in *CHRNA3*.

Smoking behavior and nicotine dependence are multifactorial traits with substantial genetic influences[3]. There is an urgent need to better understand the molecular neurobiology of nicotine dependence in order to design targeted, more effective therapies[4]. Recently, genome-wide association studies (GWAS) have established one locus associated with nicotine dependence and smoking quantity, which implicates a cluster of three genes, *CHRNA5*, *CHRNA3* and *CHRNB4* on chromosome 15q25, which encode neuronal nicotinic acetylcholine receptor subunits[5–9]. This locus

Genome Wide Association with Cigarettes per Day
A Proxy for Nicotine Use Disorder

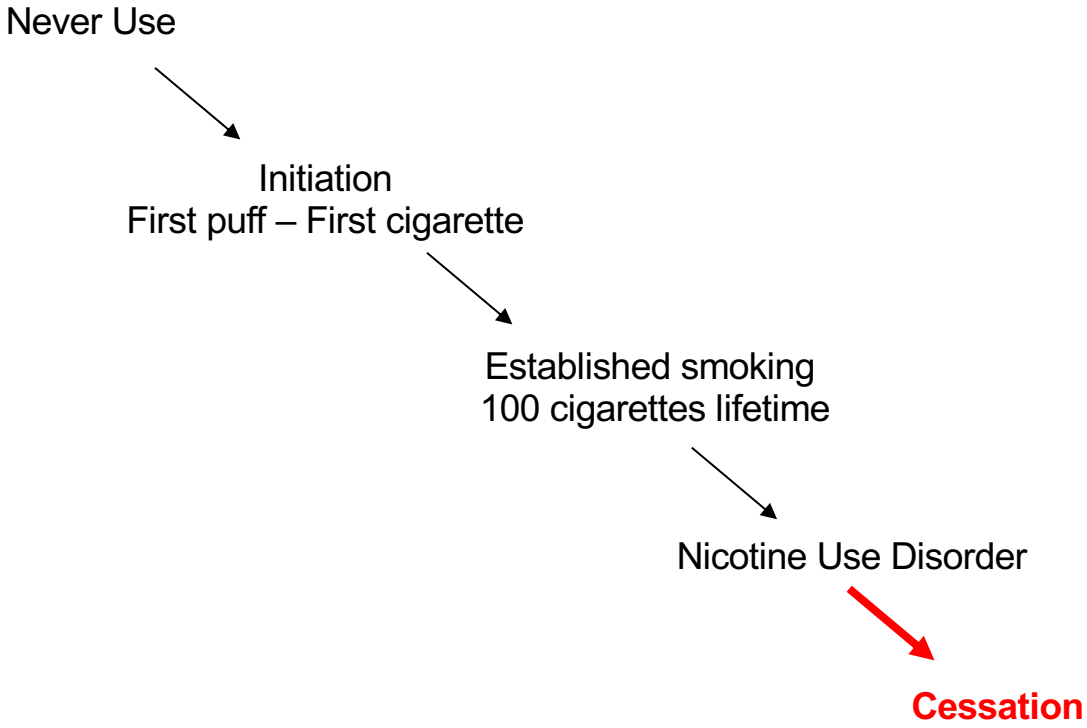


GSCAN Consortium., 2018

Chapter 4

Cessation – the ultimate goal

Smoking Cessation



Genetic Variants Predict Smoking Cessation Success

Article

Interplay of Genetic Risk Factors (*CHRNA5-CHRNA3-CHRNB4*) and Cessation Treatments in Smoking Cessation Success

Li-Shiun Chen, M.D., M.P.H., Sc.D.

Timothy B. Baker, Ph.D.

Megan E. Piper, Ph.D.

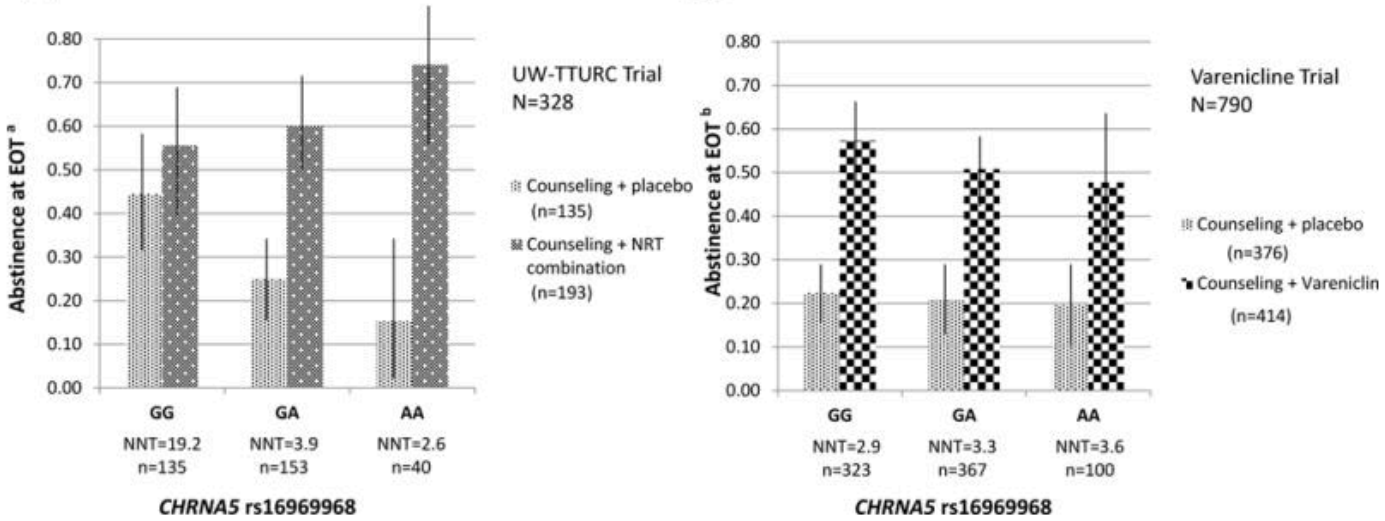
Naomi Breslau, Ph.D.

Objective: Smoking is highly intractable, and the genetic influences on cessation are unclear. Identifying the genetic factors affecting smoking cessation could elucidate the nature of tobacco dependence, enhance risk assessment, and support development of treatment algorithms. This study tested whether variants in the nico-

Results: The genetic variants in the *CHRNA5-CHRNA3-CHRNB4* region that predict nicotine dependence also predicted a later age at smoking cessation in the community sample. In the smoking cessation trial, haplotype predicted abstinence at end of treatment in individuals receiving placebo but not among individuals re-

Genetic Variation *(CHRNA5)*, Medication (Combination Nicotine Replacement Therapy vs. Varenicline) and Smoking Cessation*

Li-Shiun Chen[1,2], **Timothy B. Baker**[3], **Douglas Jorenby**[3], **Megan Piper**[3], **Nancy Saccone**[4], **Eric Johnson**[5], **Naomi Breslau**[6], **Dorothy Hatsukami**[7], **Robert M. Carney**[1], and **Laura J. Bierut**[1,2]



JNCI JOURNAL of the NATIONAL CANCER INSTITUTE

CHRNA5 Risk Variant Predicts Delayed Smoking Cessation and Earlier Lung Cancer Diagnosis—A Meta-Analysis

Li-Shiun Chen, Rayjean J. Hung, Timothy Baker, Amy Horton, Rob Culverhouse, Nancy Saccone, Iona Cheng, Bo Deng, Younghun Han, Helen M. Hansen, Janet Horsman, Claire Kim, Sharon Lutz, Albert Rosenberger, Katja K. Aben, Angeline S. Andrew, Naomi Breslau, Shen-Chih Chang, Aida Karina Dieffenbach, Hendrik Dienemann, Brittni Frederiksen, Jiali Han, Dorothy K. Hatsukami, Eric O. Johnson, Mala Pande, Margaret R. Wrensch, John McLaughlin, Vidar Skaug, Henricus F. van der Heijden, Jason Wampfler, Angela Wenzlaff, Penella Woll, Shanbeh Zienolddiny, Heike Bickeböller, Hermann Brenner, Eric J. Duell, Aage Haugen, Joachim Heinrich, John E. Hokanson, David J. Hunter, Lambertus A. Kiemeney, Philip Lazarus, Loic Le Marchand, Geoffrey Liu, Jose Mayordomo, Angela Risch, Ann G. Schwartz, Dawn Teare, Xifeng Wu, John K. Wiencke, Ping Yang, Zuo-Feng Zhang, Margaret R. Spitz, Peter Kraft, Christopher I. Amos, Laura J. Bierut

Median age of smoking cessation

Low genetic risk 52 years

High genetic risk 56 years

Median age of lung cancer diagnosis

Low genetic risk 65 years

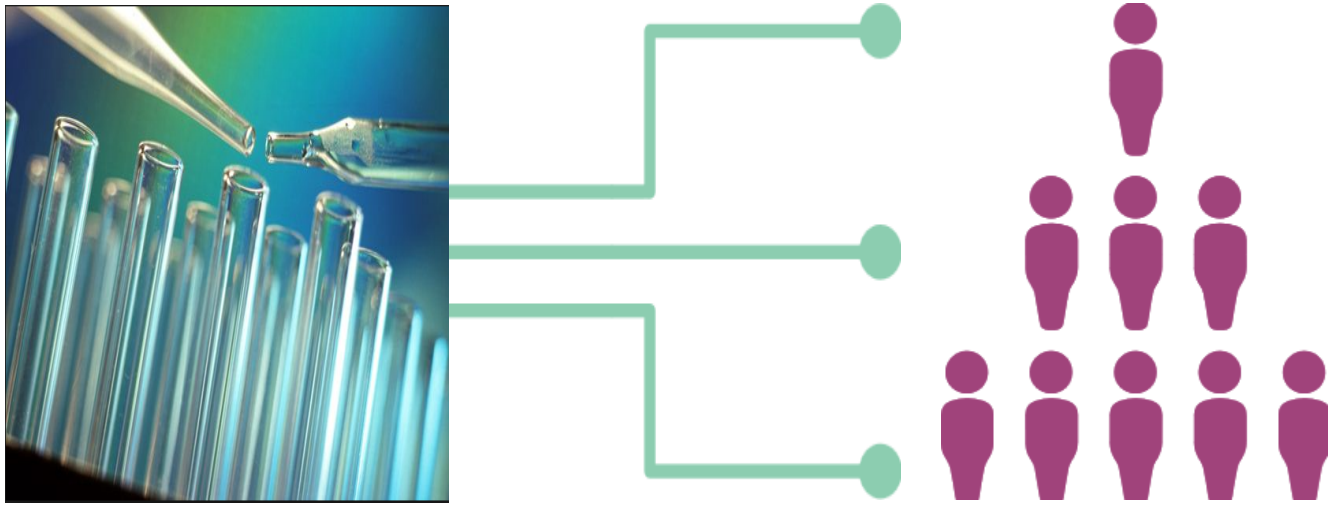
High genetic risk 61 years

Chapter 5

On the road to precision health

The Challenge…

moving science into the community



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About our data | About us

UK Biobank dataset - Demographics and sample characteristics by smoking status

		Smoking status	
	Total	**Current**	**Former**
N	142,973	40,988	101,985
Age (years)	57.5 ± 7.9	54.8 ± 8.1	58.6 ± 7.5
Sex, n (%)			
Female	65,383 (45.7)	19,138 (46.7)	46,245 (45.3)
Male	77,590 (54.3)	21,850 (53.3)	55,740 (54.7)
Education (years)	13.2 ± 5.1	12.6 ± 5.0	13.5 ± 5.2
Age started smoking (years)	17.3 ± 3.6	17.5 ± 4.3	17.2 ± 3.3
Duration smoked (years)	26.6 ± 12.9	37.3 ± 9.0	22.3 ± 11.6
Pack years of smoking	24.5 ± 19.2	29.9 ± 19.3	22.3 ± 18.8

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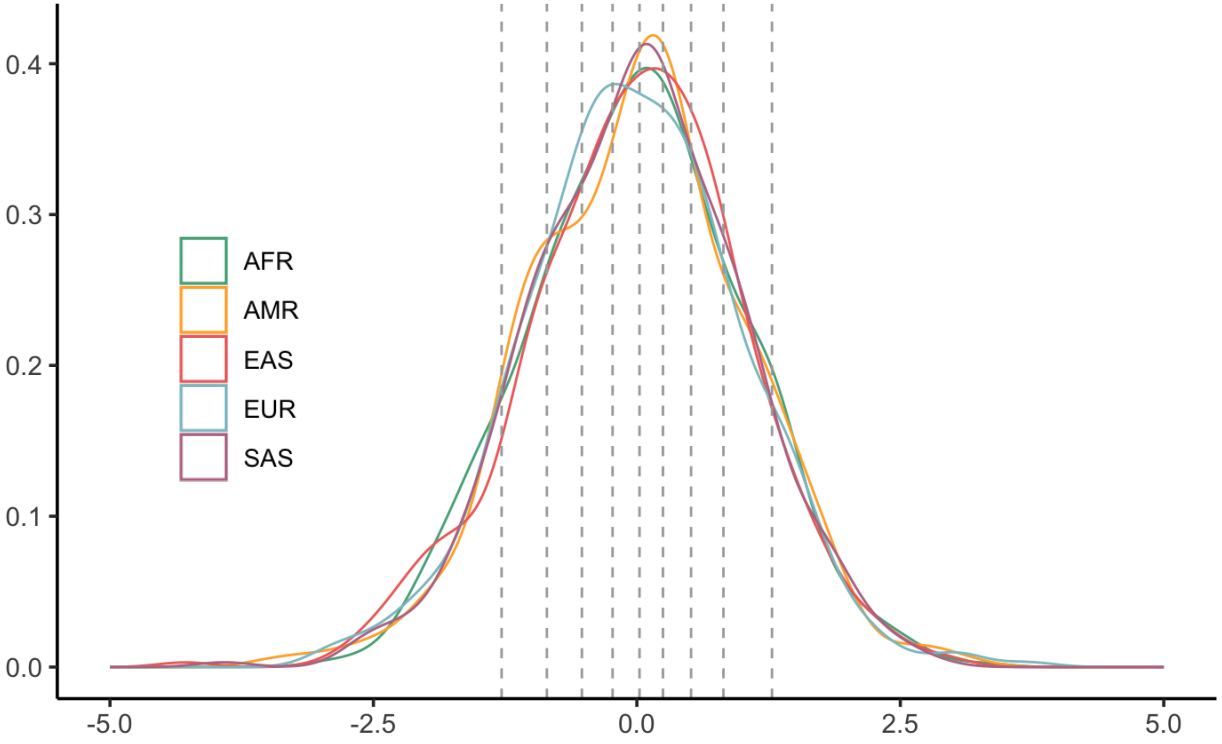
How to apply genetic knowledge into precision health

- Complex behaviors and diseases occur as a result of many genomic variants, paired with environmental influences.

- A polygenic score tells you how a person's genomic risk compares to others.

Across a population, a polygenic score is a normal distribution

- Over 100,000 variants contribute to our genetic profile.



People with a higher polygenic risk are more likely to continue smoking at age 40, 50, and 60

Polygenic score decile	Proportion continued smoking		
	Age 40	Age 50	Age 60
Bottom 10%	0.41	0.18	0.04
10-20%	0.42	0.20	0.05
20-30%	0.44	0.21	0.06
30-40%	0.47	0.23	0.07
40-50%	0.50	0.28	0.10
50-60%	0.55	0.34	0.14
60-70%	0.62	0.44	0.24
70-80%	0.74	0.59	0.41
80-90%	0.86	0.78	0.67
Top 10%	0.96	0.93	0.90

People with a higher polygenic risk are more likely to continue smoking at age 40, 50, and 60

Polygenic score decile	Proportion continued smoking		
	Age 40	Age 50	Age 60
Bottom 10%	0.41	0.18	0.04
10-20%	0.42	0.20	0.05
20-30%	0.44	0.21	0.06
30-40%	0.47	0.23	0.07
40-50%	0.50	0.28	0.10
50-60%	0.55	0.34	0.14
60-70%	0.62	0.44	0.24
70-80%	0.74	0.59	0.41
80-90%	0.86	0.78	0.67
Top 10%	0.96	0.93	0.90

People with a higher polygenic risk are more likely to continue smoking at age 40, 50, and 60

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We selected a threshold of the lower 60% of risk

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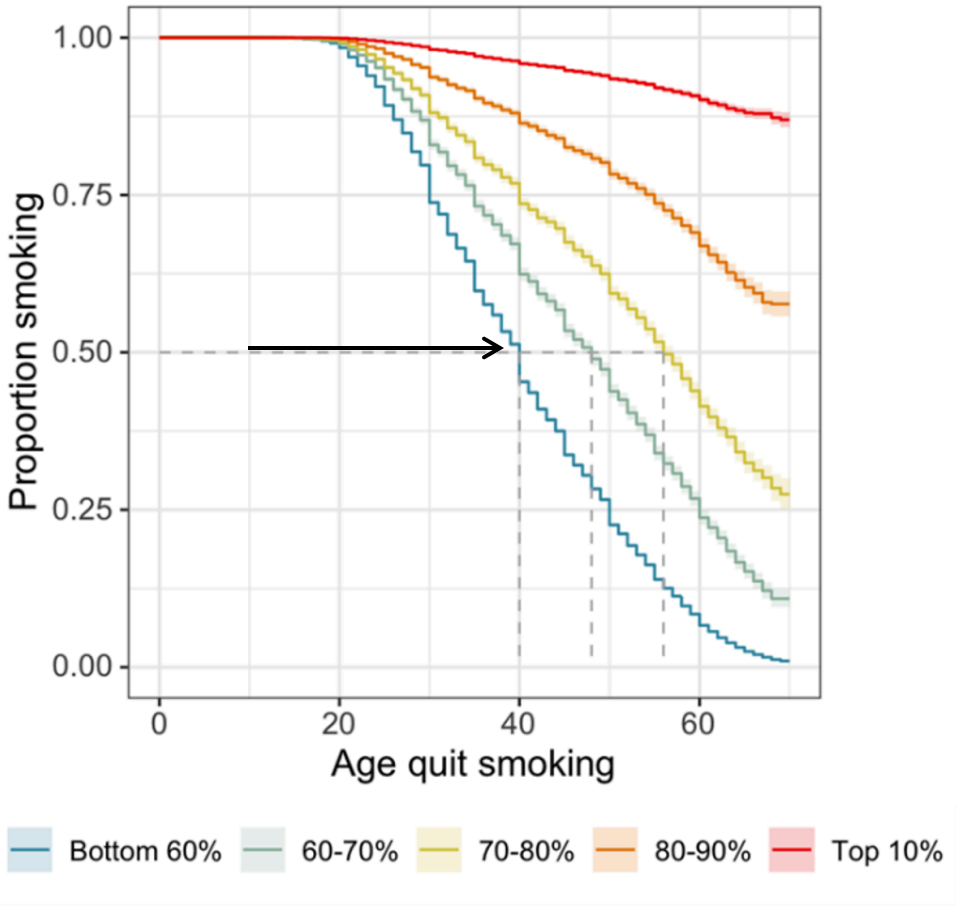
Proportion smoking by polygenic score

The lowest polygenic score group - lowest 60%, by age 40 half have quit smoking and by age 60 most have quit.



Proportion smoking by polygenic score

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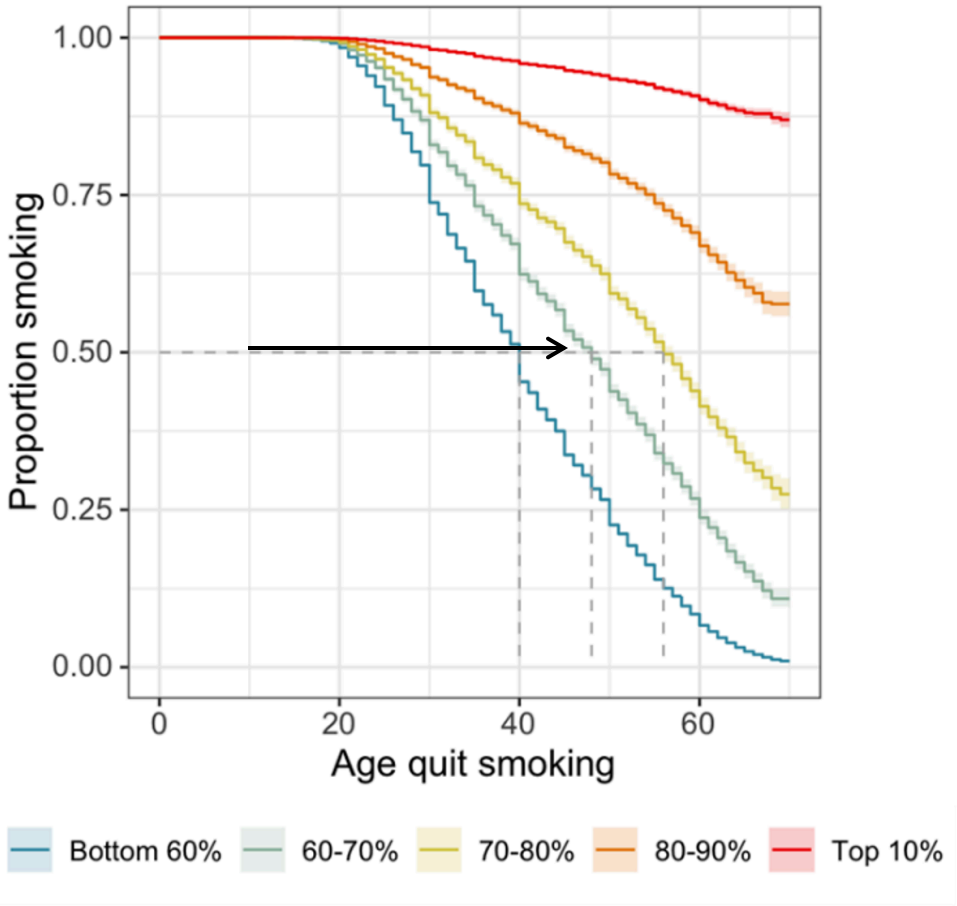
60% - 70% group –

Median age of quitting smoking is 48



Proportion smoking by polygenic score

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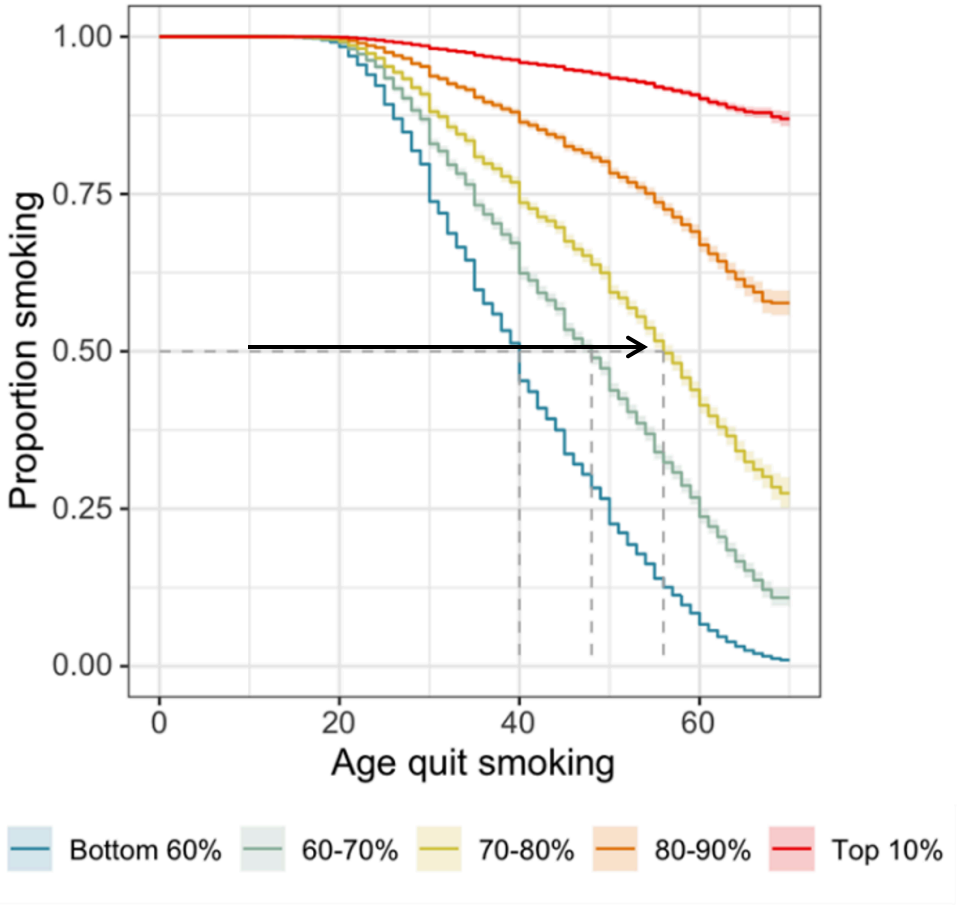
60% - 70% group –
Median age of quitting smoking is 48

70% - 80% group –

Median age of quitting smoking is 56



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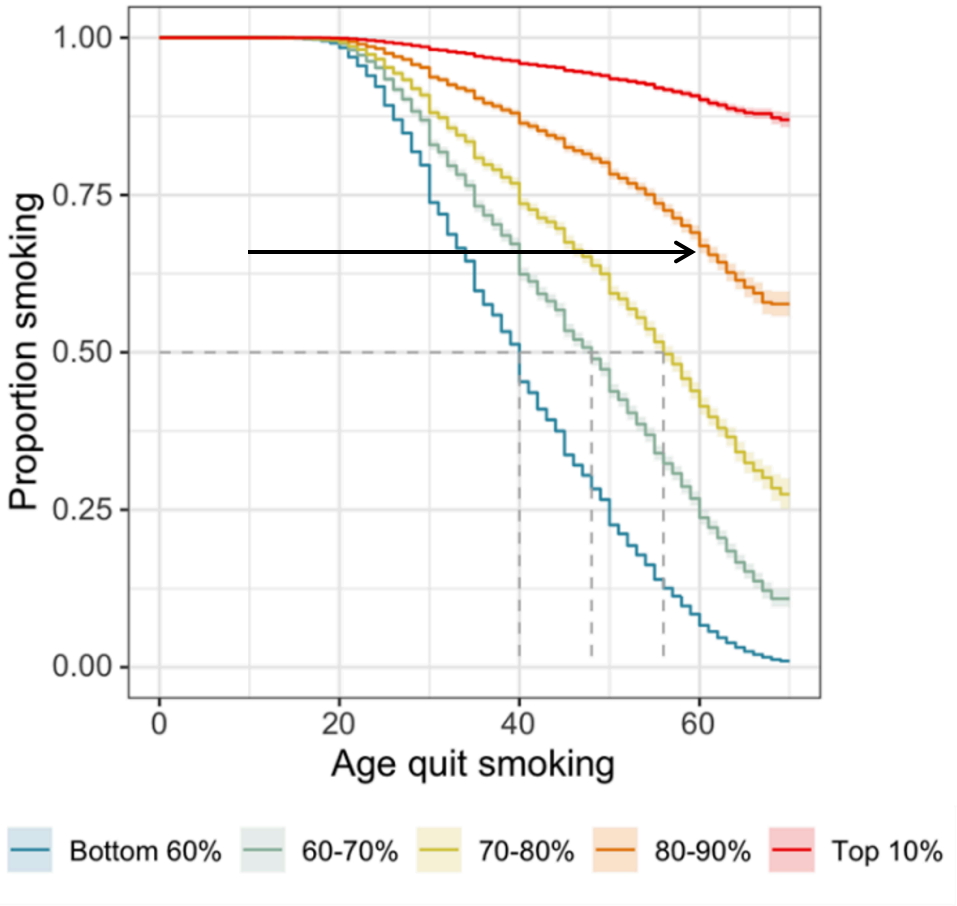
60%- 70% group –
Median age of quitting smoking is 48

70%-80% group –
Median age of quitting smoking is 56

80% - 90% group –

At age 60, 67% continue to smoke



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60%- 70% group –
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Median age of quitting smoking is 56

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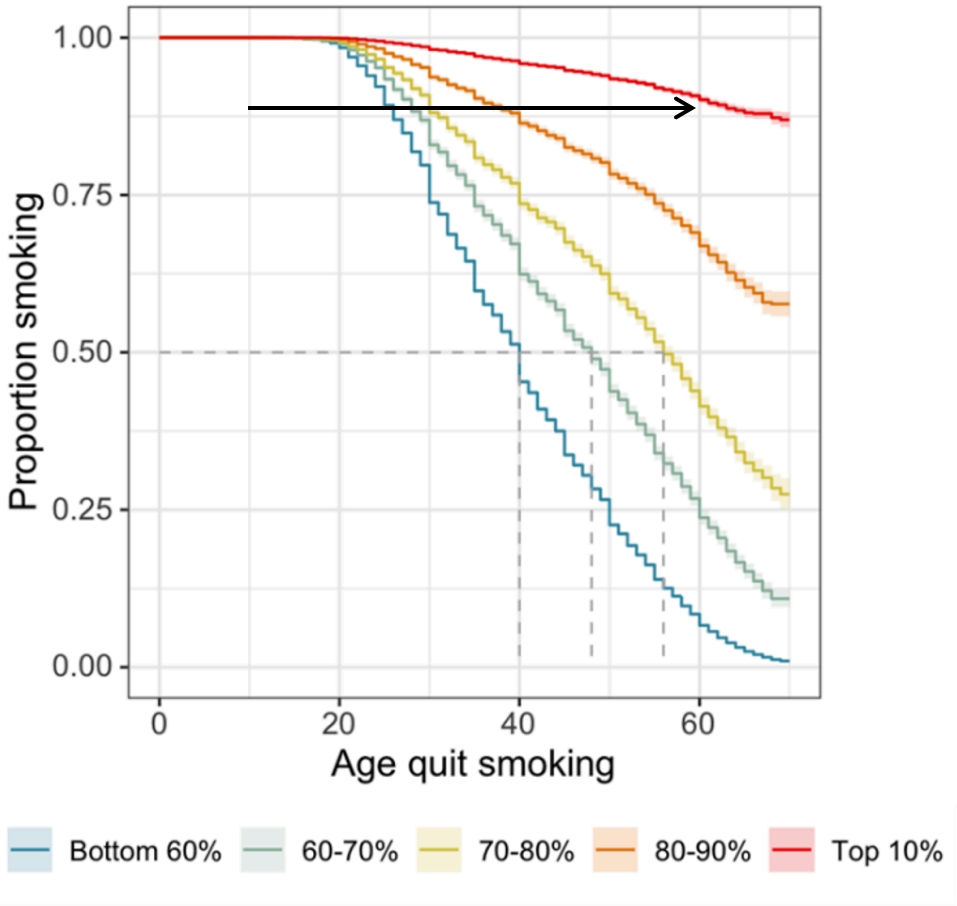
At age 60, 67% continue to smoke

Top 10% -

At age 60, 90% continue to smoke



When do you bring a test into clinical care

- ✓ Analytic validity
- ✓ Clinical validity
- ✓ Clinical utility
- ✓ Ethical and social issues

When do you bring a test into clinical care

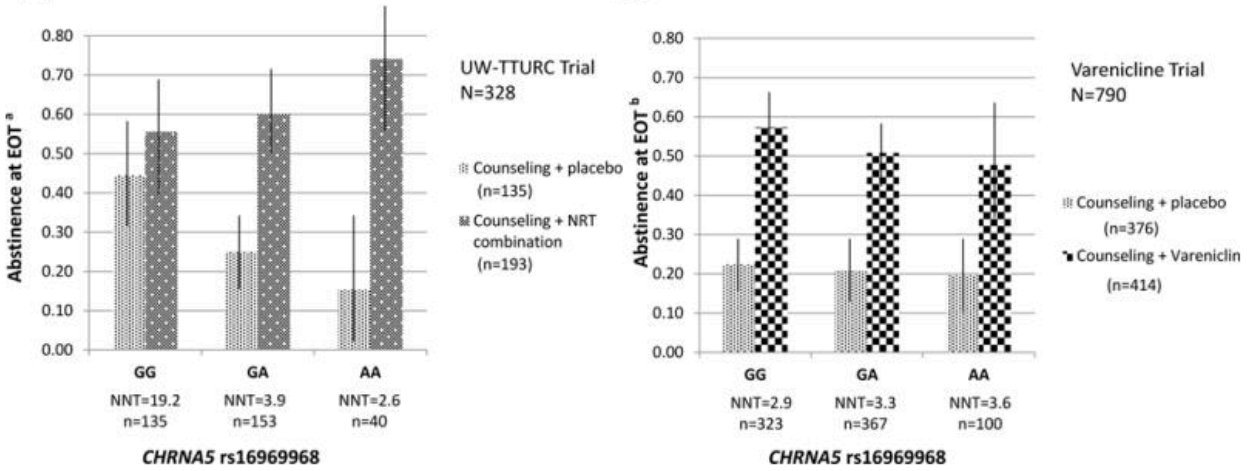
- ✓ Analytic validity

When do you bring a test into clinical care

- ✓ Analytic validity
- ✓ Clinical validity

When do you bring a test into clinical care

- ✓ Analytic validity
- ✓ Clinical validity
- ✓ Clinical utility



When do you bring a test into clinical care

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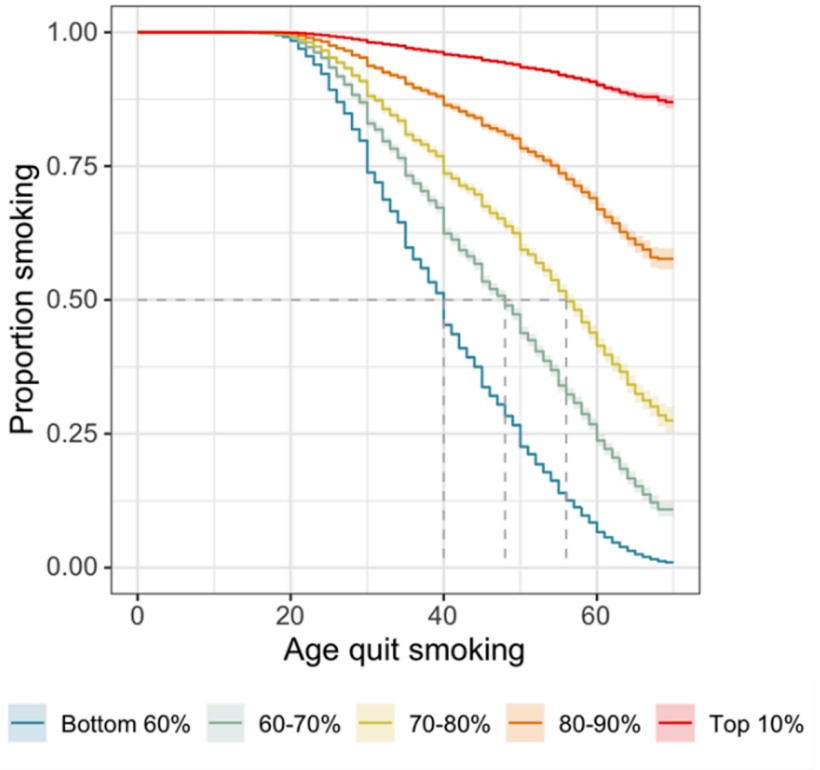

When do you bring a test into clinical care

- ✓ Analytic validity
- ✓ Clinical validity
- ✓ Clinical utility
- ✓ Ethical and social issues

The time is now for precision health

- A person's genetic variation predicts their difficulty quitting smoking and smoking related health outcomes.
- Those at highest genetic risk need to strongest treatment to successfully quit smoking.
- Should we consider harm reduction strategies for those at highest genetic risk?

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GENEVA Project

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Michael Fiore

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Jay Tischfield

Southwest Foundation

Laura Almasy

Virginia Commonwealth University

Danielle Dick

Phenotypic and genetic data are available to qualified investigators through the NIDA Genetics Consortium and dbGaP.


Washington
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