

Scientific perspectives for predictive personalized medicine in the era of next-generation genomic sequencing

Sérgio D.J. Pena, MD, PhD, FRCP(C)
Professor of Biochemistry and Director of the
Clinical Genomics Laboratory of the
Universidade Federal de Minas Gerais,
Belo Horizonte, Brazil



sdpena@gmail.com

CELEBRATING 125 YEARS OF EXPLORATION

Siberian Paradise | **MI**
RGM.COM

NATIONAL GEOGRAPHIC

WILL LI



Afghanistan:
Racing to
Save Lives

Toyota:
The Fall of
An Icon



TIN
The Science of
Living Longer

SPECIAL
22-PAGE
HEALTH
SECTION



THREE
GENERATIONS
of a Family
Kirkus, 37;
Grandmother Lulu, 65

FEBRUARY 26, 2014

The Iran Opportunity By Fareed
Zakaria / E-Cigarettes / \$20K Homes

TIME

CAN
Google
SOLVE

DEATH?

The search giant is launching a venture
to extend the human life span.

That would be crazy—if it weren't Google
By Harry McCracken and Lew Grossman



**Onie Ponder
111 yo**



**Otis Clark
106 yo**



**Irving Kahn
104 yo**
**Helen Reichert
108 yo**



Health is a state of complete physical, mental, and social well being, and not merely the absence of disease or infirmity



Healthy Aging



Oxymoron

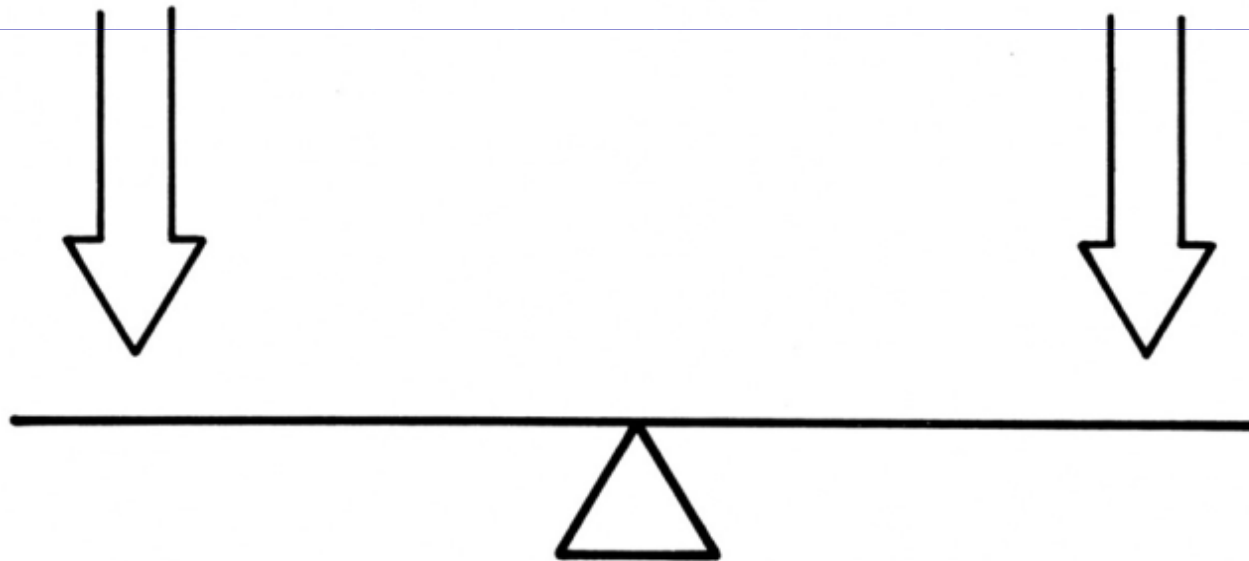
Disease-free Aging

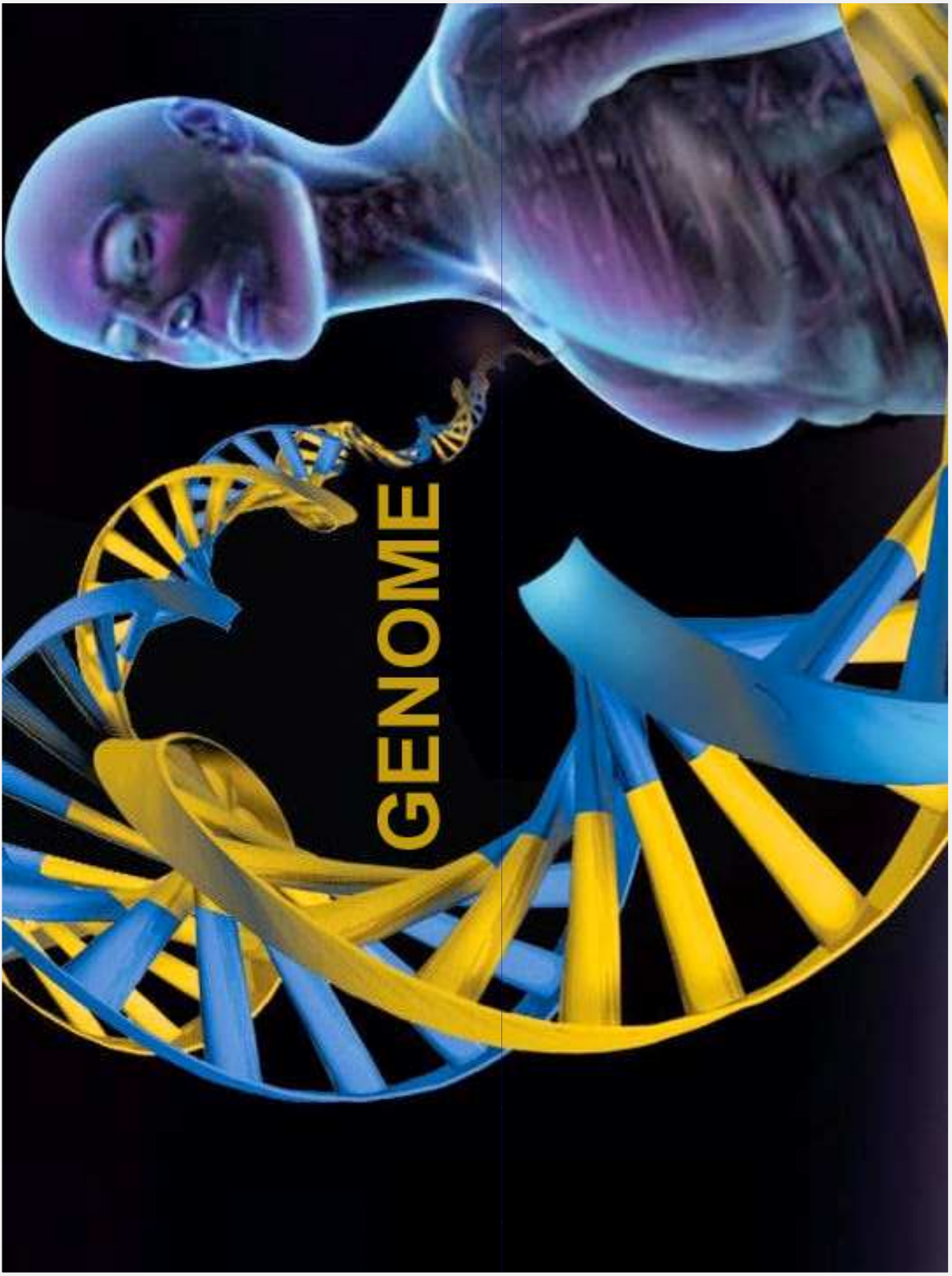


Being free of disease depends on a virtuous equilibrium between genome and environment

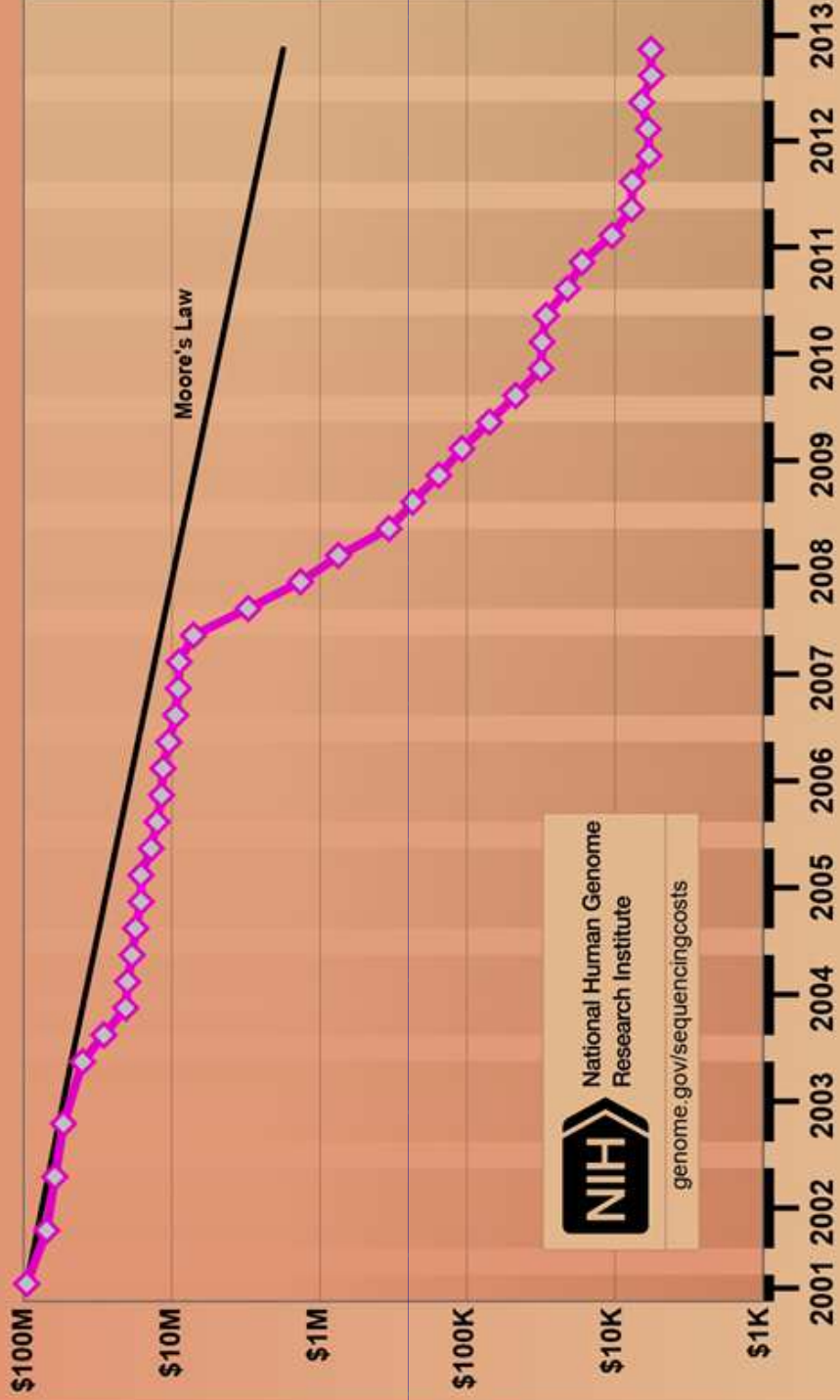
Genome

Environment



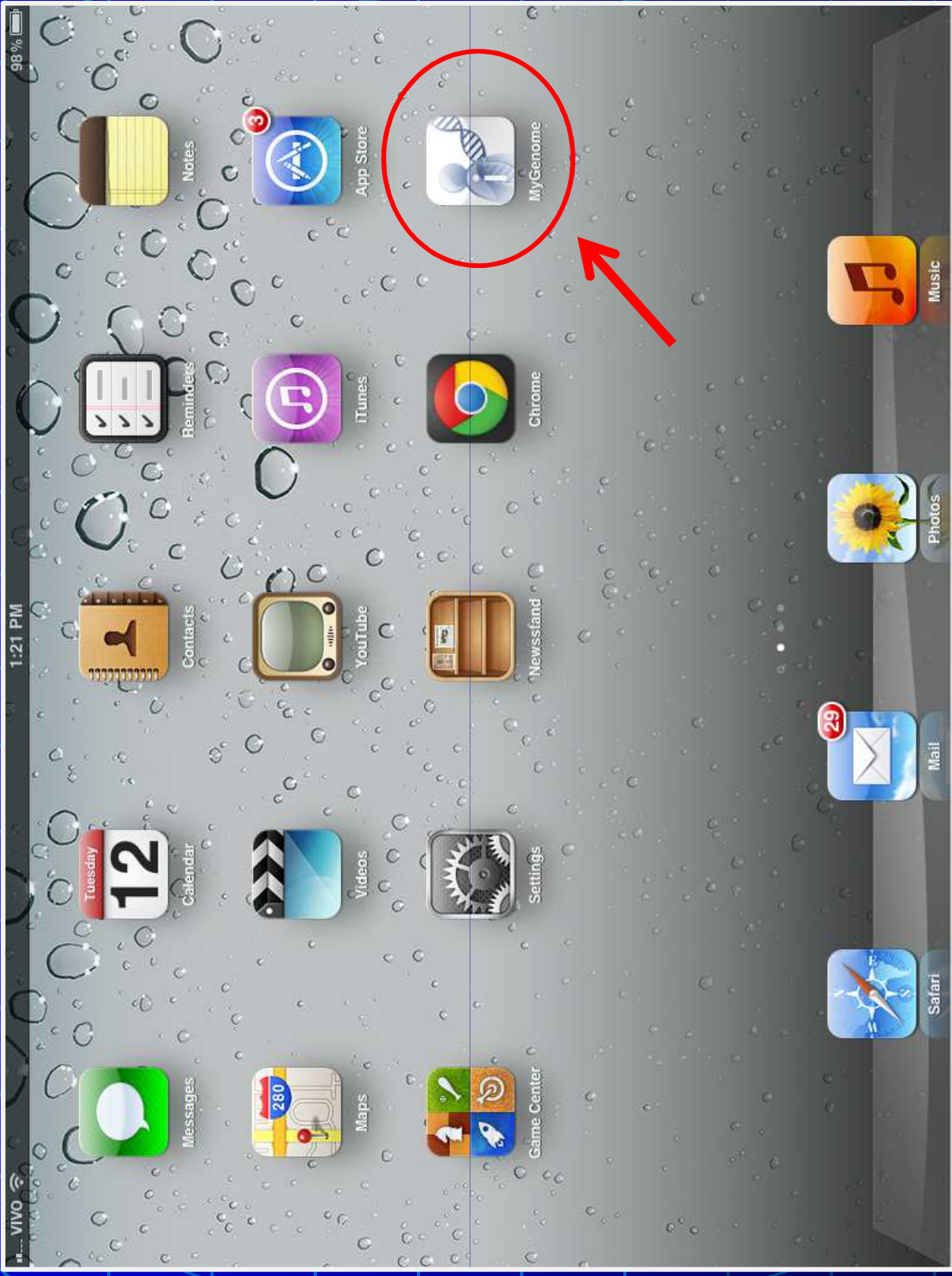


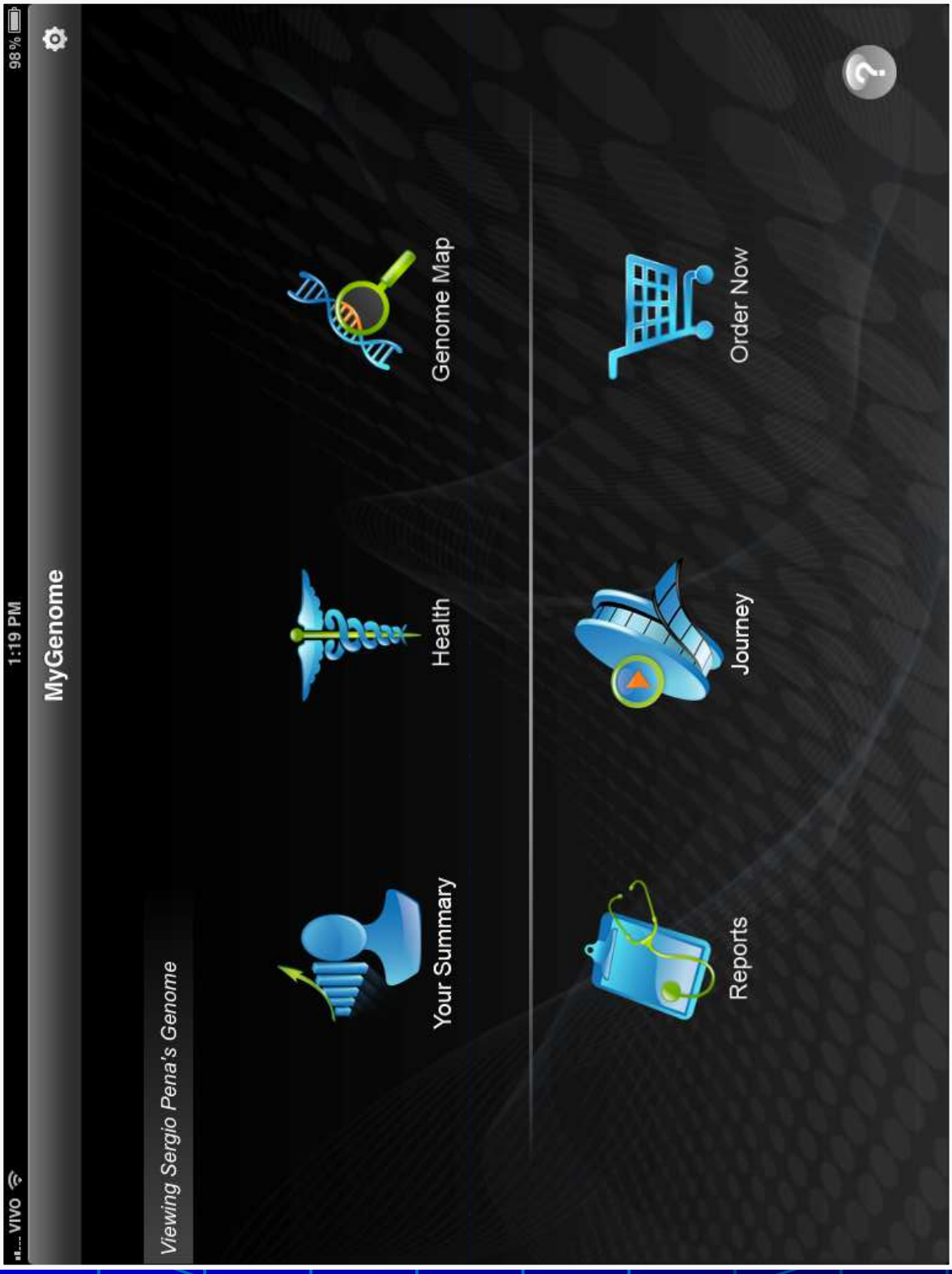
Cost per Genome



National Human Genome
Research Institute

genome.gov/sequencingcosts





VIVO 98% 1:19 PM



MyGenome

Viewing Sergio Pena's Genome



Your Summary



Health



Genome Map



Reports



Journey



Order Now



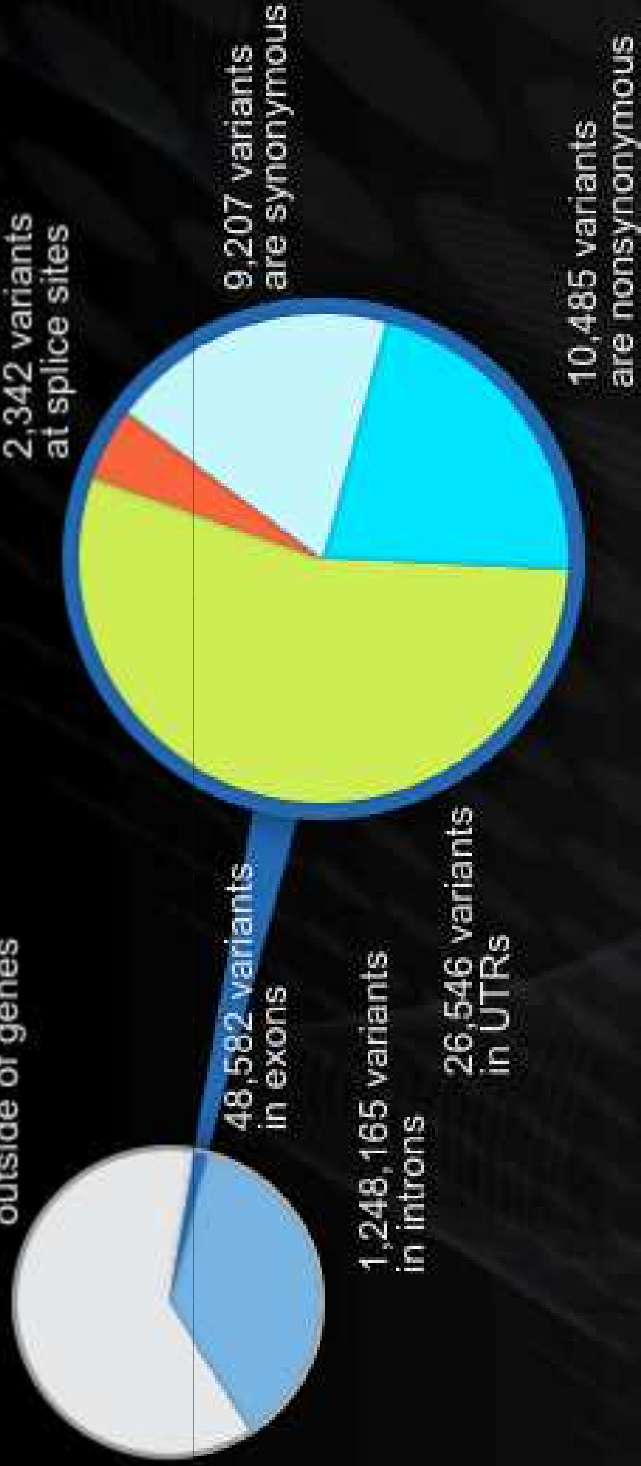
Your variants distribution

3,388,786 variants were identified in your genome.



2,092,039 variants
outside of genes

2,342 variants
at splice sites



LETTER

96 | NATURE | VOL 488 | 2 AUGUST 2012

doi:10.1038/nature11283

A mutation in *APP* protects against Alzheimer's disease and age-related cognitive decline

Thorlakur Jonsson¹, Jasvinder K. Atwal², Stacy Steinberg¹, Jon Snaedal³, Palmi V. Jonsson^{3,8}, Sigurbjorn Bjornsson³, Hreinn Stefansson¹, Patrick Sulem¹, Daniel Gudbjartsson¹, Janice Maloney², Kwame Hoyte², Amy Gustafson², Yichin Liu², Yanmei Lu², Tushar Bhangale², Robert R. Graham², Johanna Huttenlocher^{1,4}, Gyda Bjornsdottir¹, Ole A. Andreassen⁵, Erik G. Jönsson⁶, Aarno Palotie⁷, Timothy W. Behrens², Olafur T. Magnusson¹, Augustine Kong¹, Unnur Thorsteinsdottir^{1,8}, Ryan J. Watts² & Kari Stefansson^{1,8}

VIVO

1:19 PM

98%

MyGenome



Viewing Sergio Pena's Genome



Your Summary



Health



Genome Map



Reports

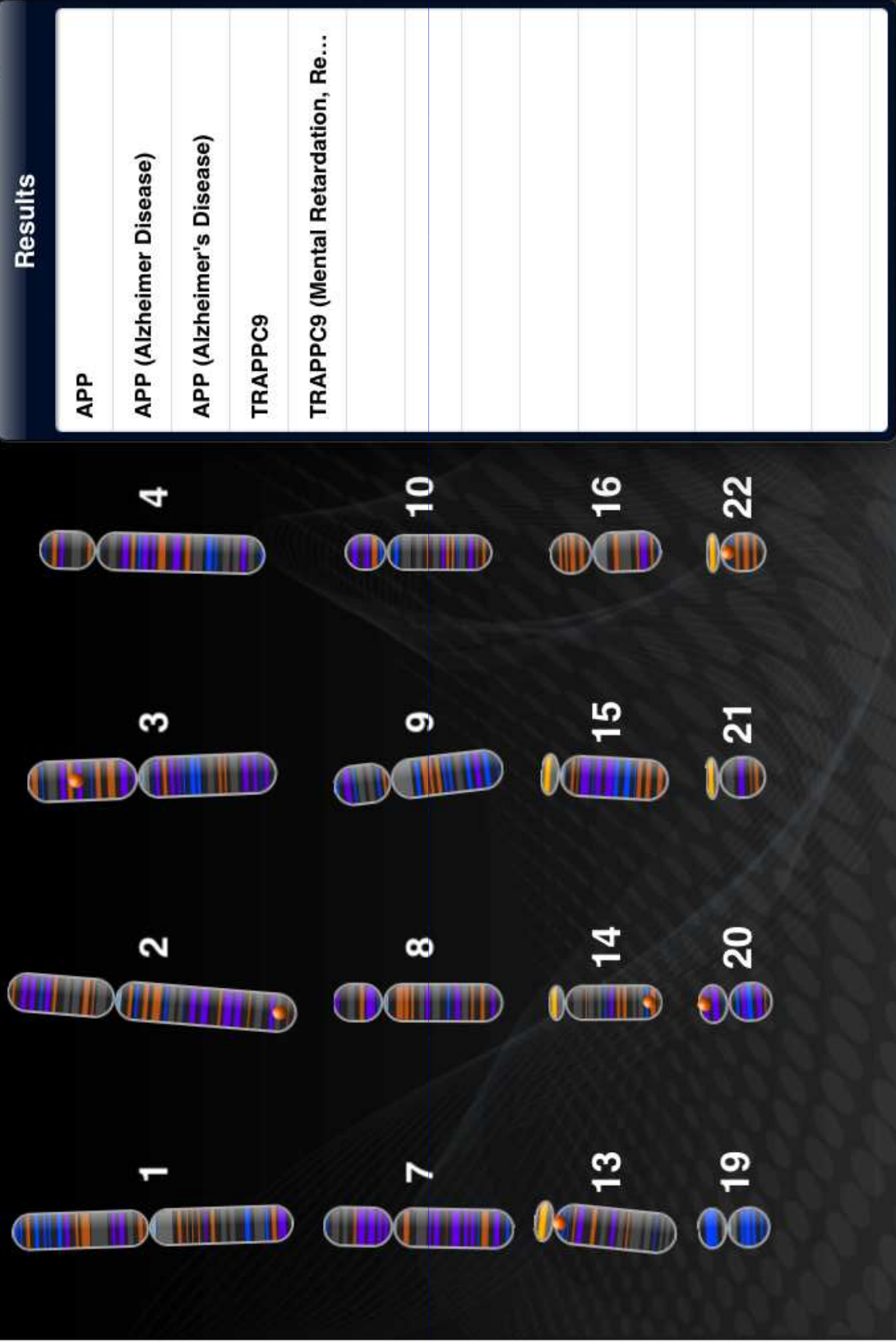


Journey



Order Now





VIVO 1:20 PM 98%

Genome Map - All Chromosomes **Chromosome 21** Search

Chromosome 21

Variants in the current genomic region

- Variant at location 27397523
- Variant at location 27397607
- Variant at location 27397823
- Variant at location 27398550
- Variant at location 27399399
- Variant at location 27401305

Information

Chromosome Statistics

- 48,129,895** Total Base Pairs
- 35,108,702** Sequenced Base Pairs
- 295** Genes

Current Selection **X**

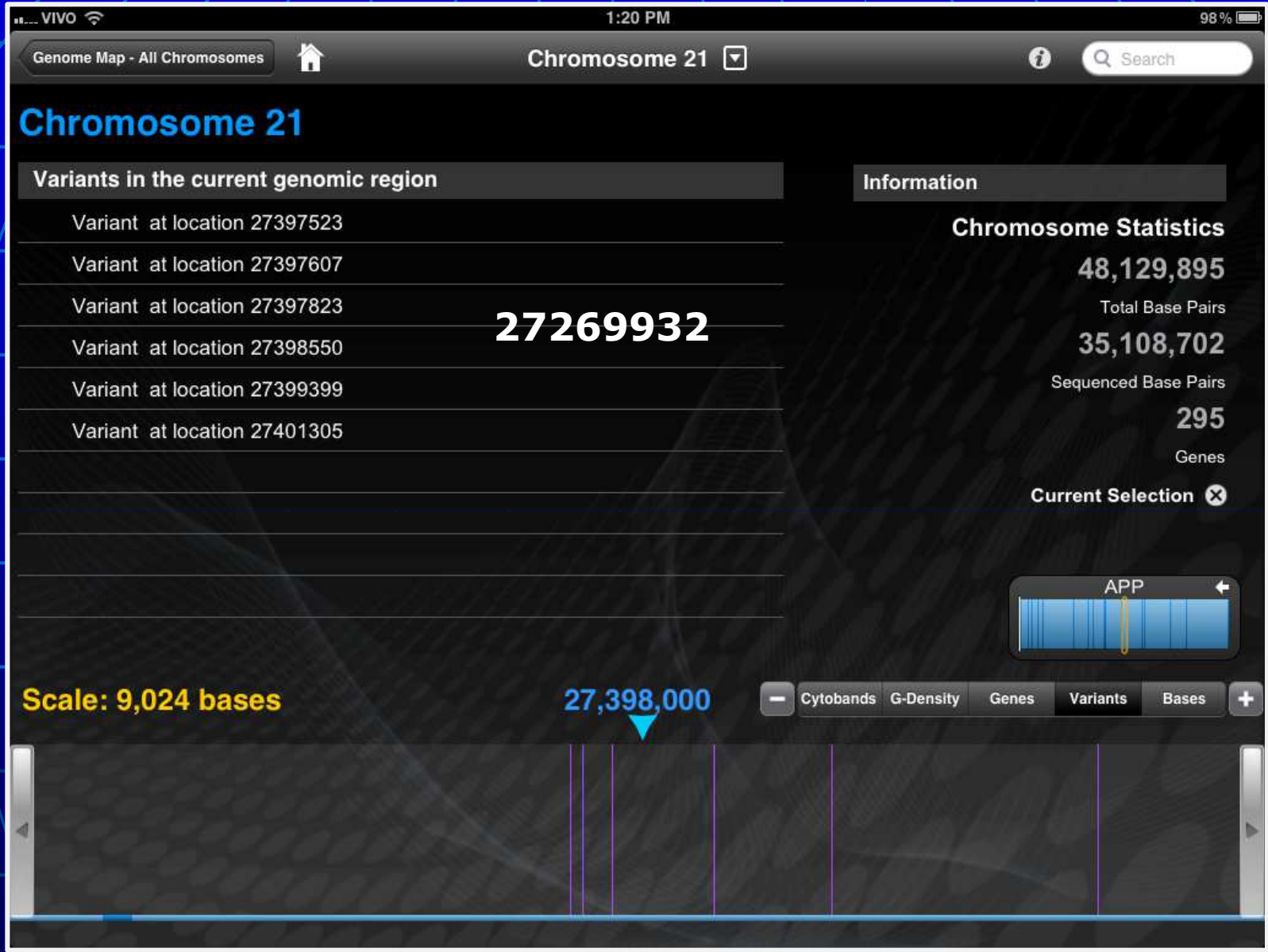
27269932

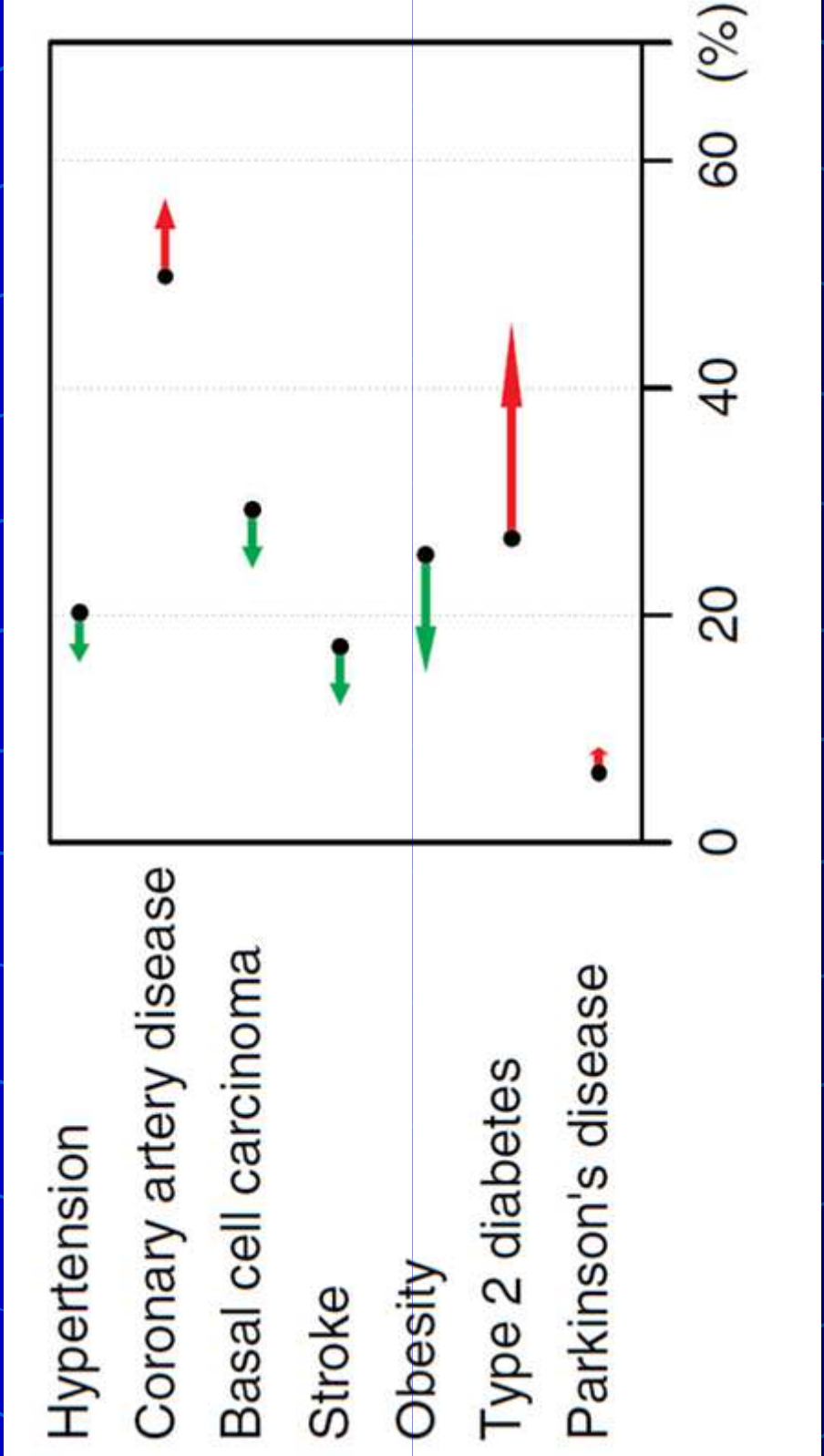
Scale: 9,024 bases

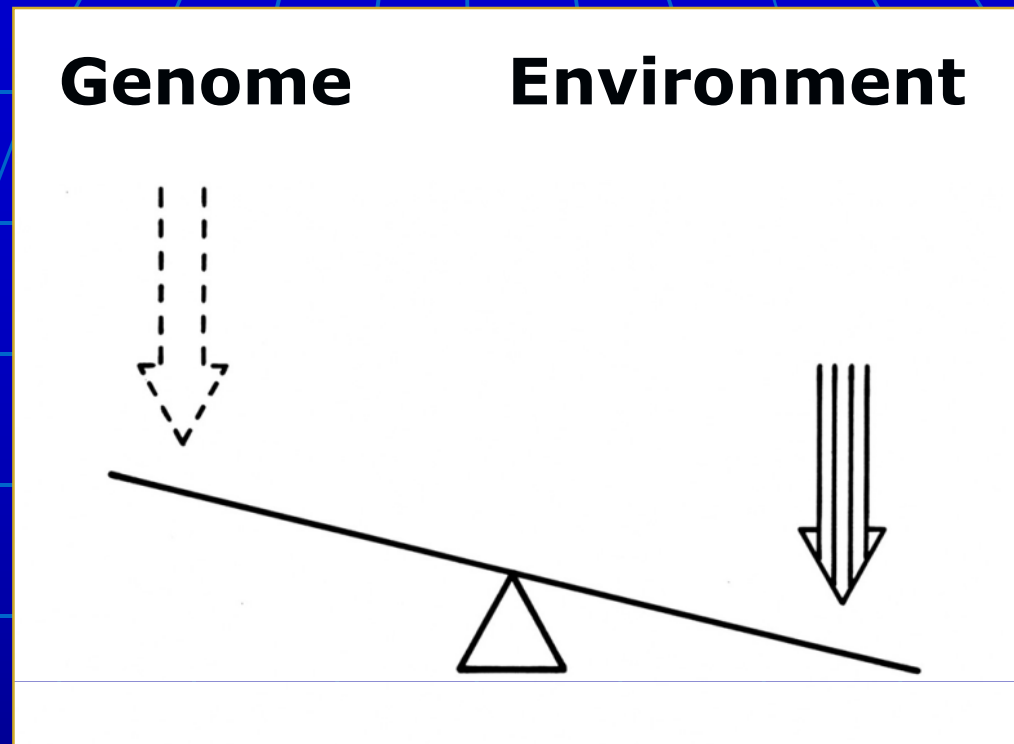
27,398,000

APP

Cytobands G-Density Genes Variants Bases







Precision Medicine aims to achieve personalized prevention through knowledge of the genome of the individual and the adaptation of the environment to it

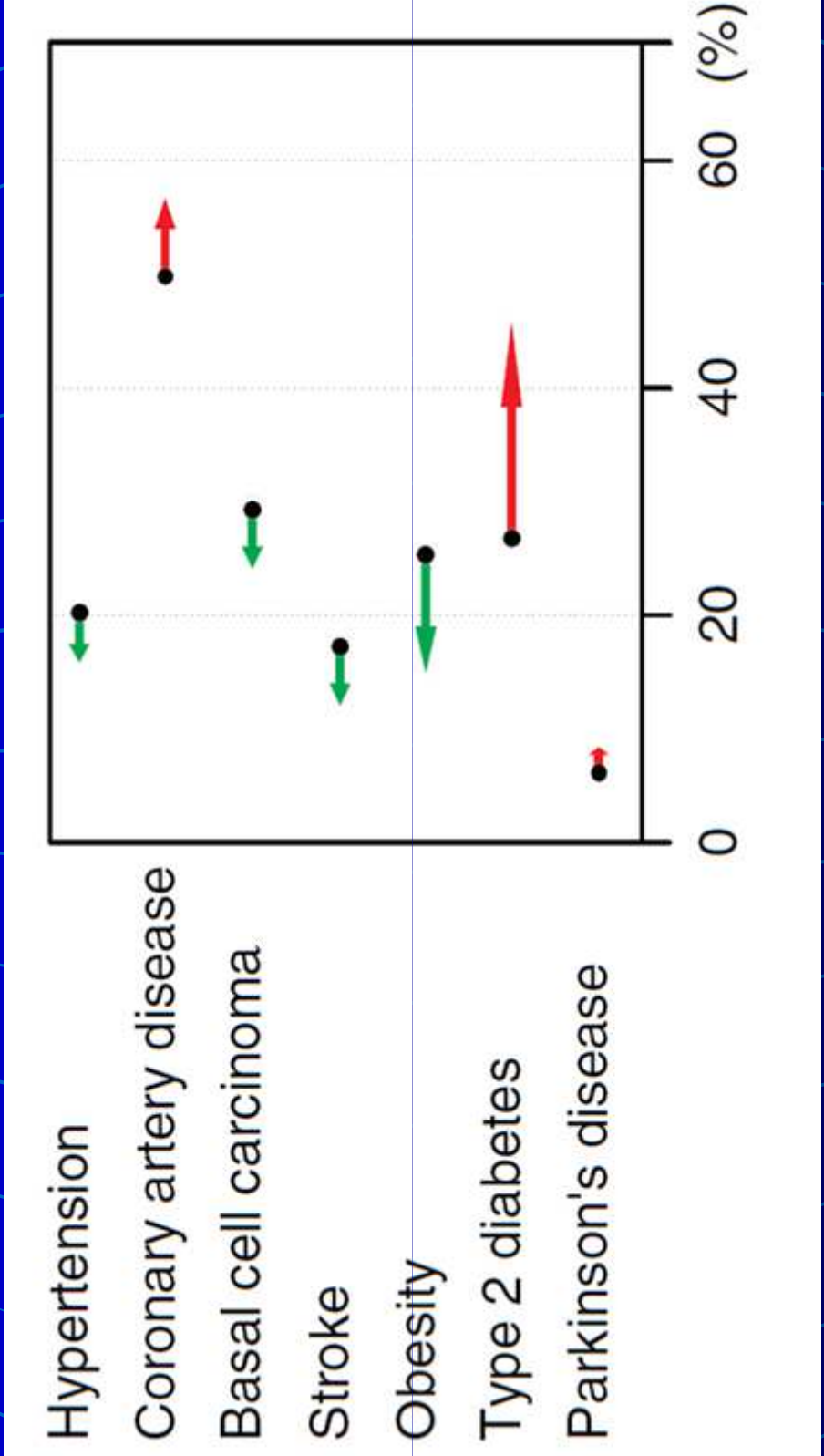
Basal Cell Carcinoma

Journal Nat Genet
Study Size ■■■
Replications None
Contrary Studies None
Applicable Ethnicities European
Marker rs7538876

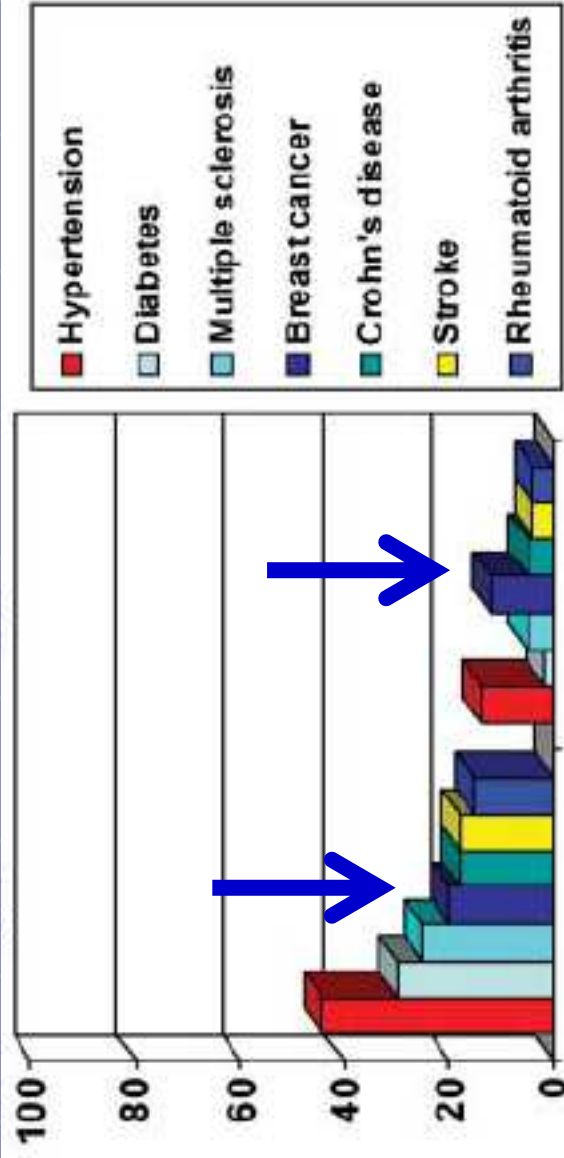
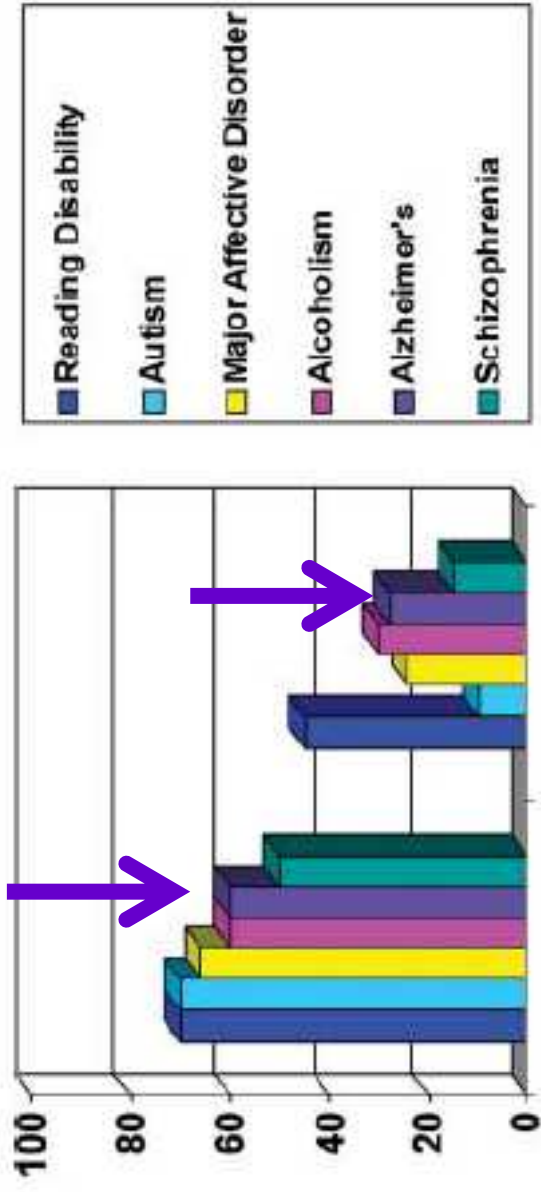
Who	Genotype	What it Means
	AA	Slightly higher odds of developing basal cell carcinoma.
	AG	Typical odds of developing basal cell carcinoma.
Sergio Pena	GG	Slightly lower odds of developing basal cell carcinoma.

Journal Nat Genet
Study Size ■■■
Replications None
Contrary Studies None
Applicable Ethnicities European
Marker rs801114

Who	Genotype	What it Means
	GG	Slightly higher odds of developing basal cell carcinoma.
	GT	Typical odds of developing basal cell carcinoma.
Sergio Pena	TT	Slightly lower odds of developing basal cell carcinoma.





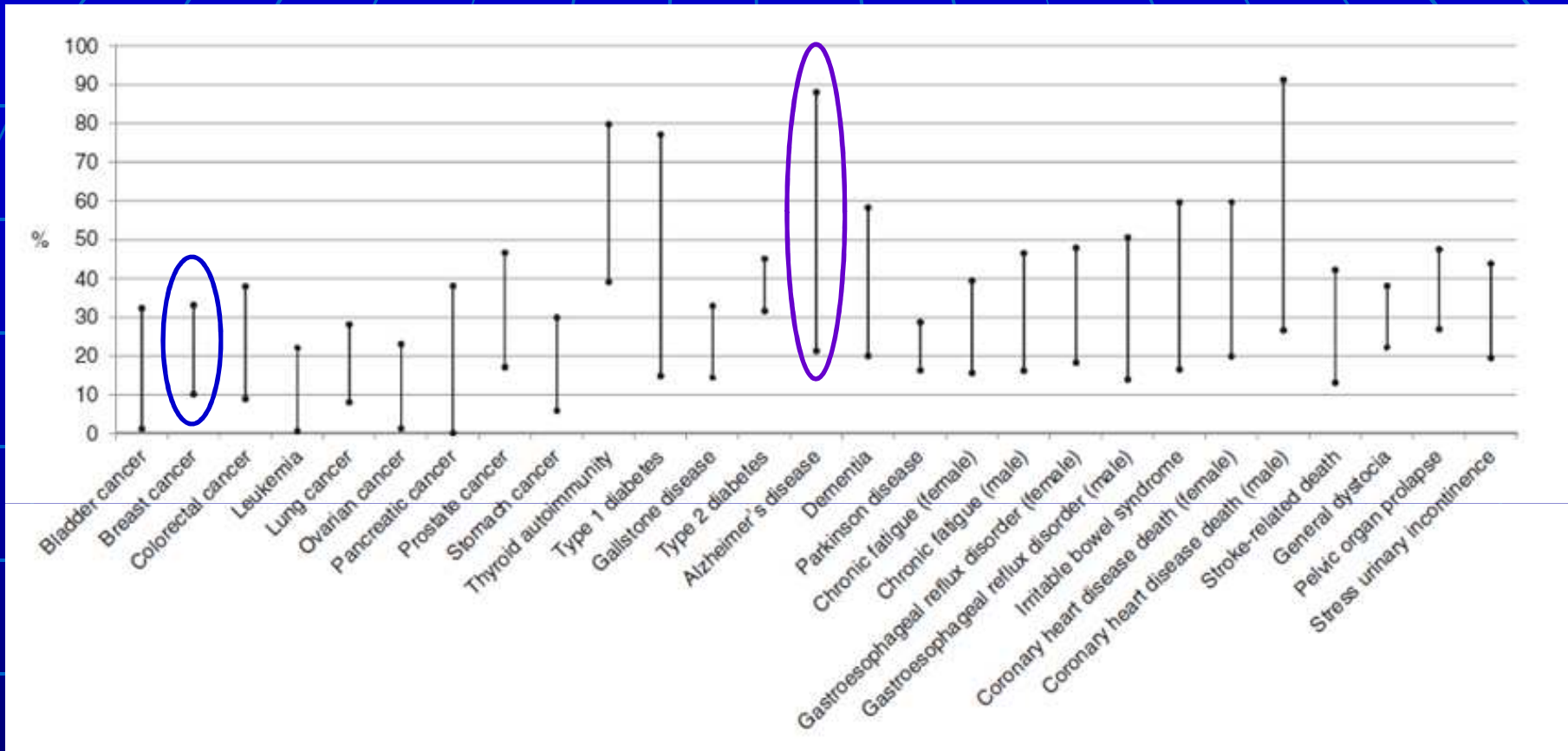


RESEARCH ARTICLE

GENOMICS

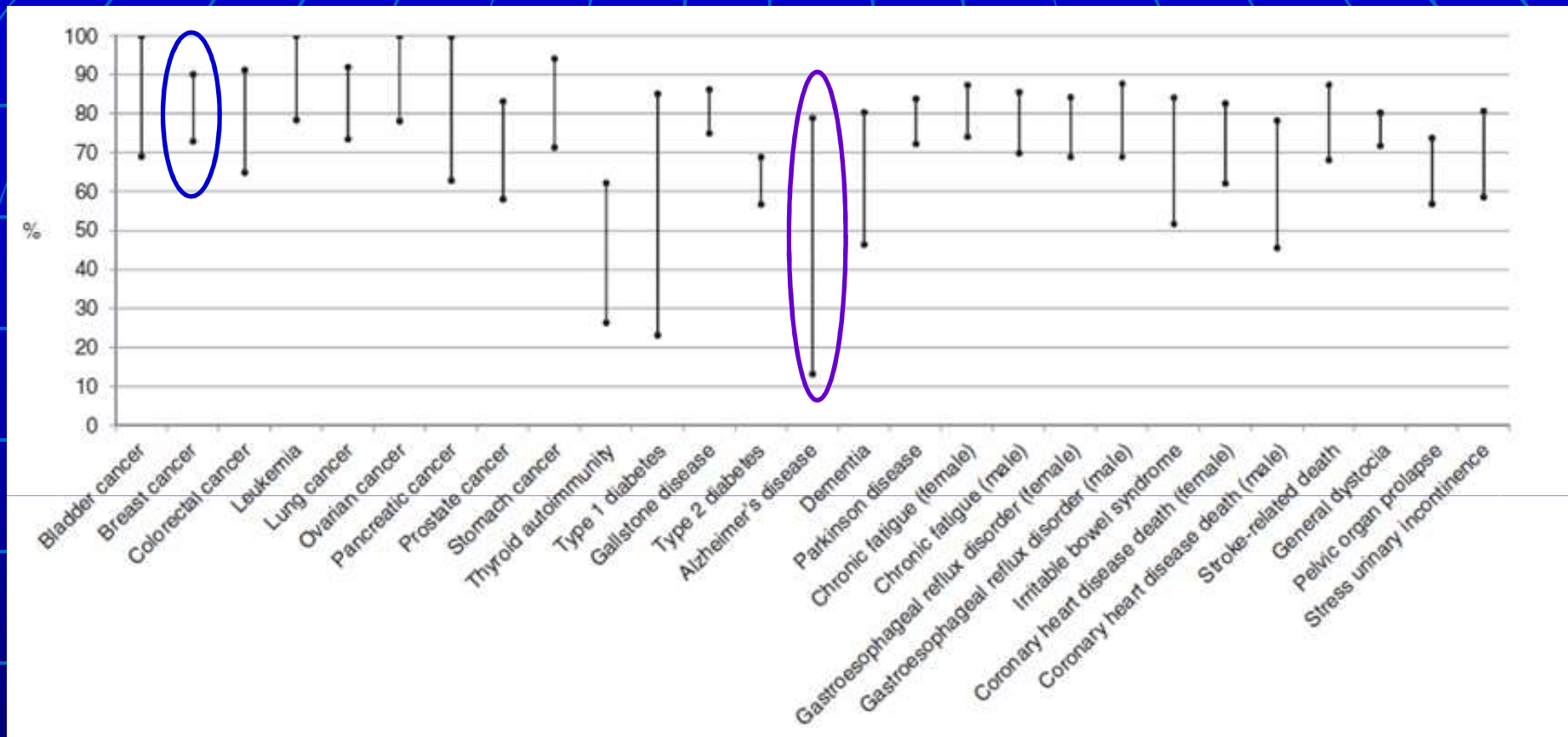
The Predictive Capacity of Personal Genome Sequencing

Nicholas J. Roberts,^{1*} Joshua T. Vogelstein,^{2*} Giovanni Parmigiani,³ Kenneth W. Kinzler,¹
Bert Vogelstein,^{1†} Victor E. Velculescu^{1†}



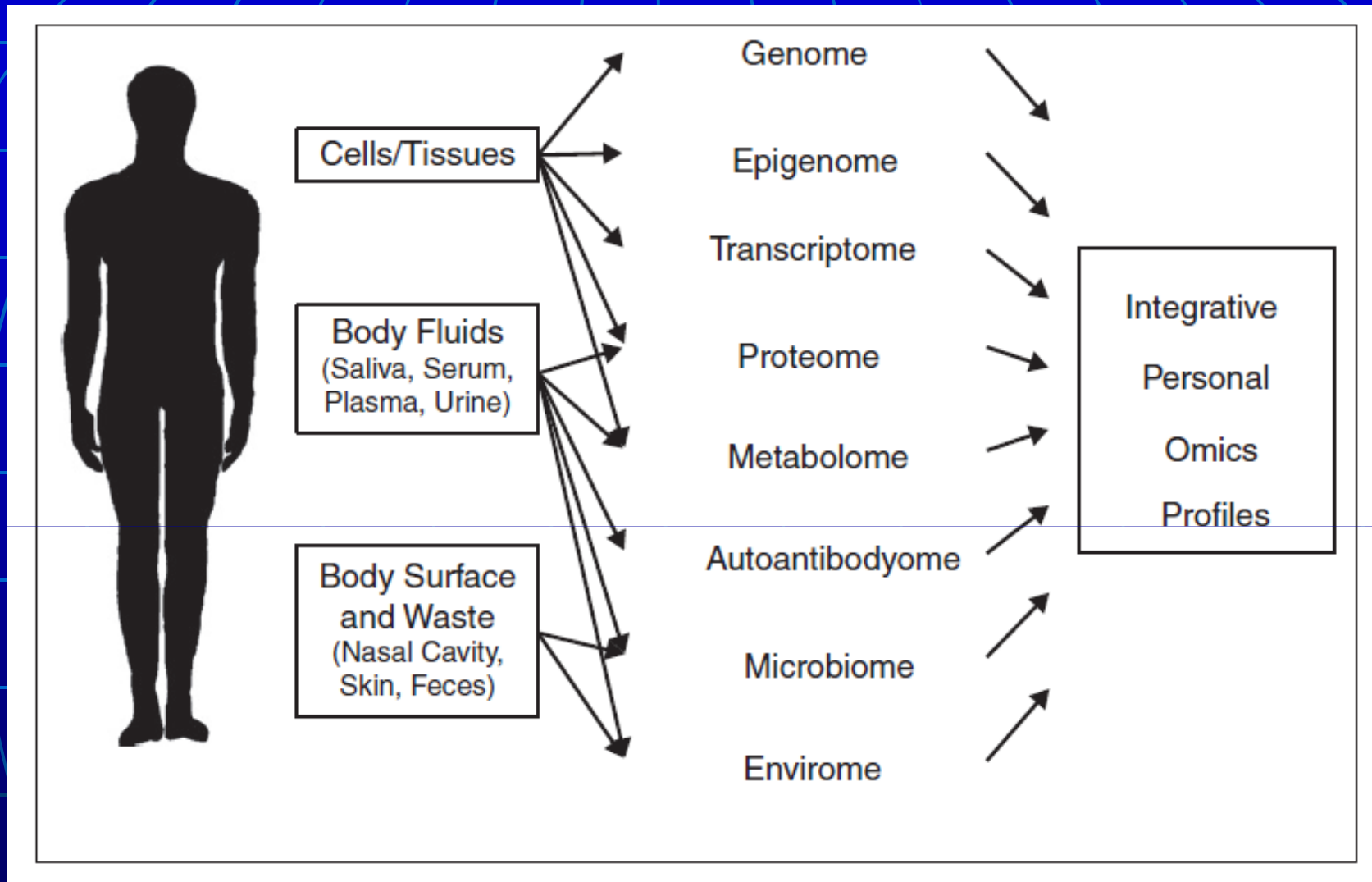
The fraction of patients with disease who would test positive by whole-genome sequencing

Roberts et al, 2012

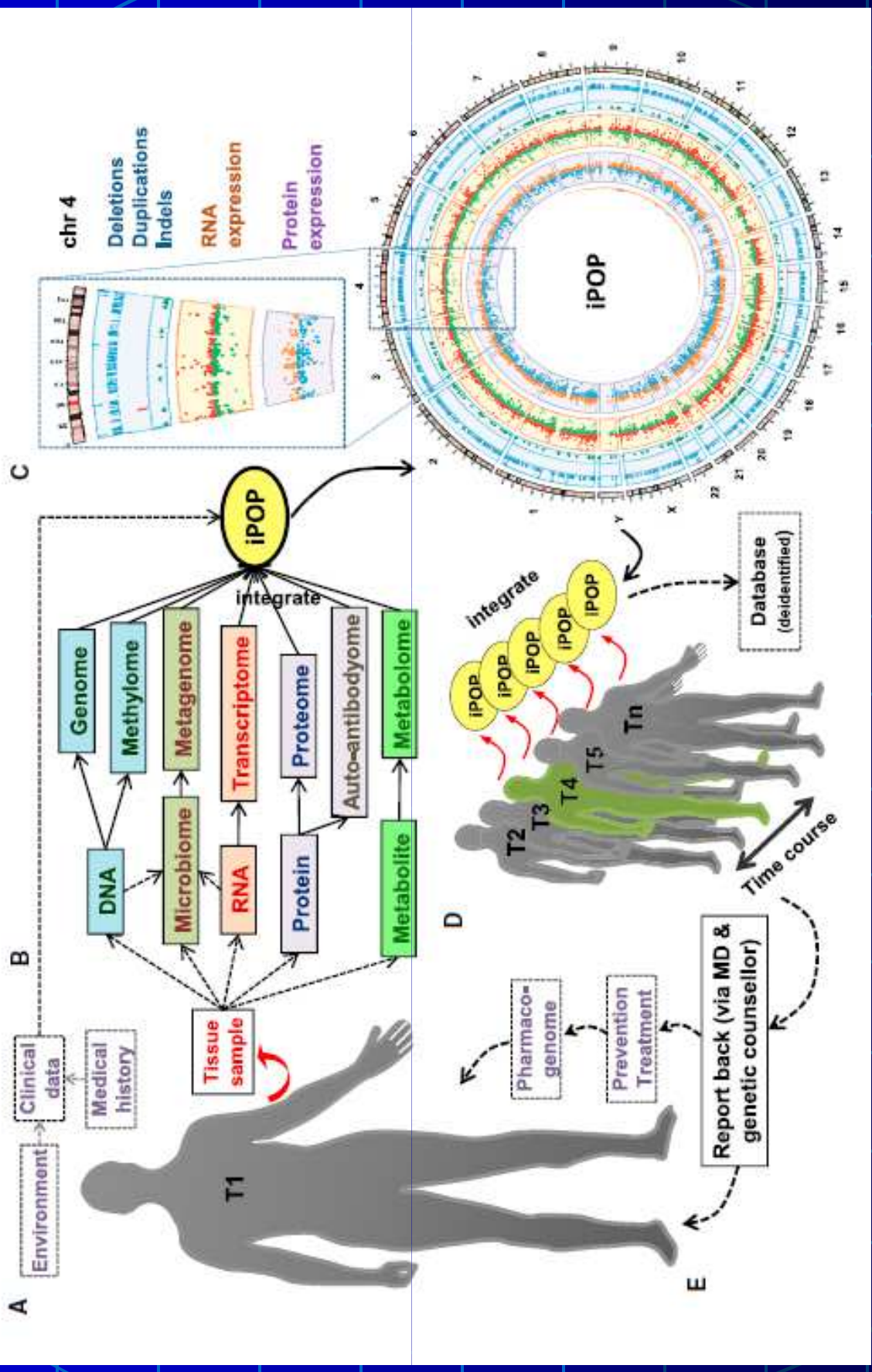


**Relative risk of disease in individuals testing negative
by whole-genome sequencing**

Roberts et al, 2012



Michael Snyder
Stanford University



Conclusion

Integrative Personal Omics Profiling (IPOP) and the new techniques of next-generation genomic sequencing are capable of equipping precision medicine with the necessary predictive and personalized tools to lead human populations into the era of disease-free aging

Caveat 1

Personal genomic sequencing is a clinical reality. The medical interpretation is difficult, but is rapidly developing and there are already very palpable clinical benefits.

However, there is evidence that alone it will not be able to leverage all the requisite predictive and preventive aspects of Precision Medicine.

Caveat 2

Integrative Personal Omics Profiling (IPOP) promises to provide the whole picture of genomic and environmental causation of human diseases necessary for the predictive and preventive components of Precision Medicine.

However, it is not yet a clinical reality.

Caveat 3

Full medical applicability of Integrative Personal Omics Profiling (IPOP) will depend on development of cost-effective methodology for the study and interpretation of the several “omes” and should be developed in the next few decades (rather than years).

Final Conclusion

Science already has all the necessary tools to implement predictive personalized precision medicine. It is expected that, in the next few decades, we will conquer chronic human diseases and usher human populations into disease-free aging.

Beyond that, developments in regenerative medicine based on human induced pluripotent stem (iPS) cells, promise to leverage a better quality of life during aging.



Thank you!

sdpena@gmail.com

Precision medicine is...

- **Personalized**
- **Predictive**
- **Proactive**
- **Preventive**
- **Participative**







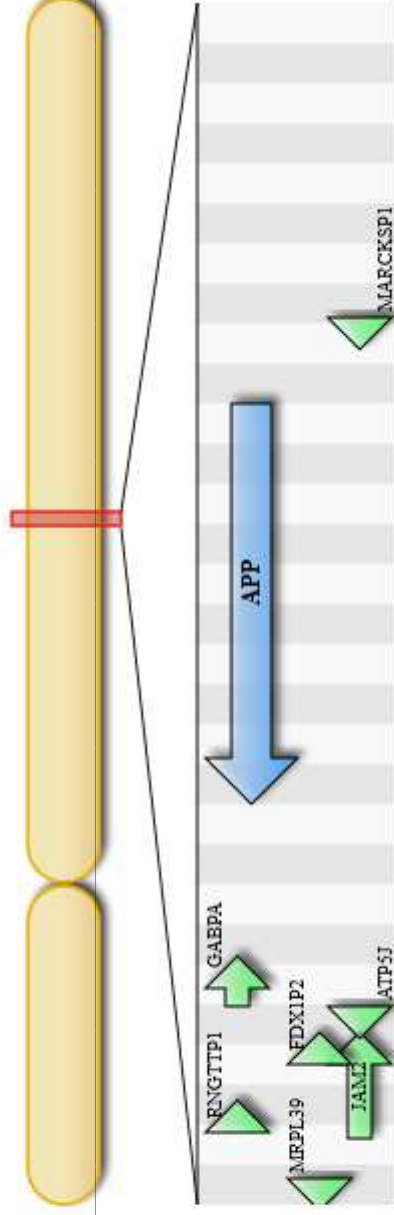
APP



Amyloid beta (A4) precursor protein

21

Goto map



Alamut: APP - Amyloid beta (A4) precursor protein

Application Edit View Web Mutations Tools Folders Shortcuts Help

Chrom. uniprot UniProt GEN. ATLAS

Go to: chr17:620-45670

APP - Amyloid beta (A4) precursor protein | GRCh37 (Chr 21)

Overview of Transcript NM_000484.3

▼ Genome - chr21:270,001-27,269,863 (GRCh37) - 139 bps

27270000 27269990 27269980 27269970 27269960 27269950 27269940 27269930 27269920 27269910 27269900 27268880 27268870

TAT ACT ACATT ATGT CC AAG ACCCAACT GTTT AT AGT CTGCCTCT AGAGACTT CACTT CT ACCT ACCTT CACTT CAAGCT GTACT GAGT CCT AT ACTT CAAGT AGT AGT TTTT AACCAT GCATTTT TATT AAAT GGAGT
TAT GAT GTAAT ACAGGT CTGGTT GACAAAAT CAAGACGGAGGAGAT CTCT GAAGT GAAGAT GGAT GCAGAAAT CCGACAT GACT CAGGAT AT GAA GTT CAT CAT CAAAAAT GGTACGTAATAATTTACCTCT

▼ Nucleotide Conservation

▼ NM_000484.3: Homo sapiens amyloid beta (A4) precursor protein (APP), transcript variant 1, mRNA.

c.1964-10 c.1964 c.1970 c.1990 c.2000 c.2010 c.2020 c.2030 c.2040 c.2050 c.2064 c.2064+10 c.2064+20

TAT GAT GTAAT ACAGGT CTGGTT GACAAAAT CAAGACGGAGGAGAT CTCT GAAGT GAAGAT GGAT GCAGAAAT CCGACAT GACT CAGGAT AT GAA GTT CAT CAT CAAAAAT GGTACGTAATAATTTACCTCT

G S G L T N I K T E I S E V K M D A E F R H D S G Y E V H Q K L

655 660 665 670 675 680 685 688

▼ dbSNP Short Variations | SwissProt Variants

c.2017 p.673

TAT GAT GTAAT ACAGGT CTGGTT GACAAAAT CAAGACGGAGGAGAT CTCT GAAGT GAAGA g.27,269,932

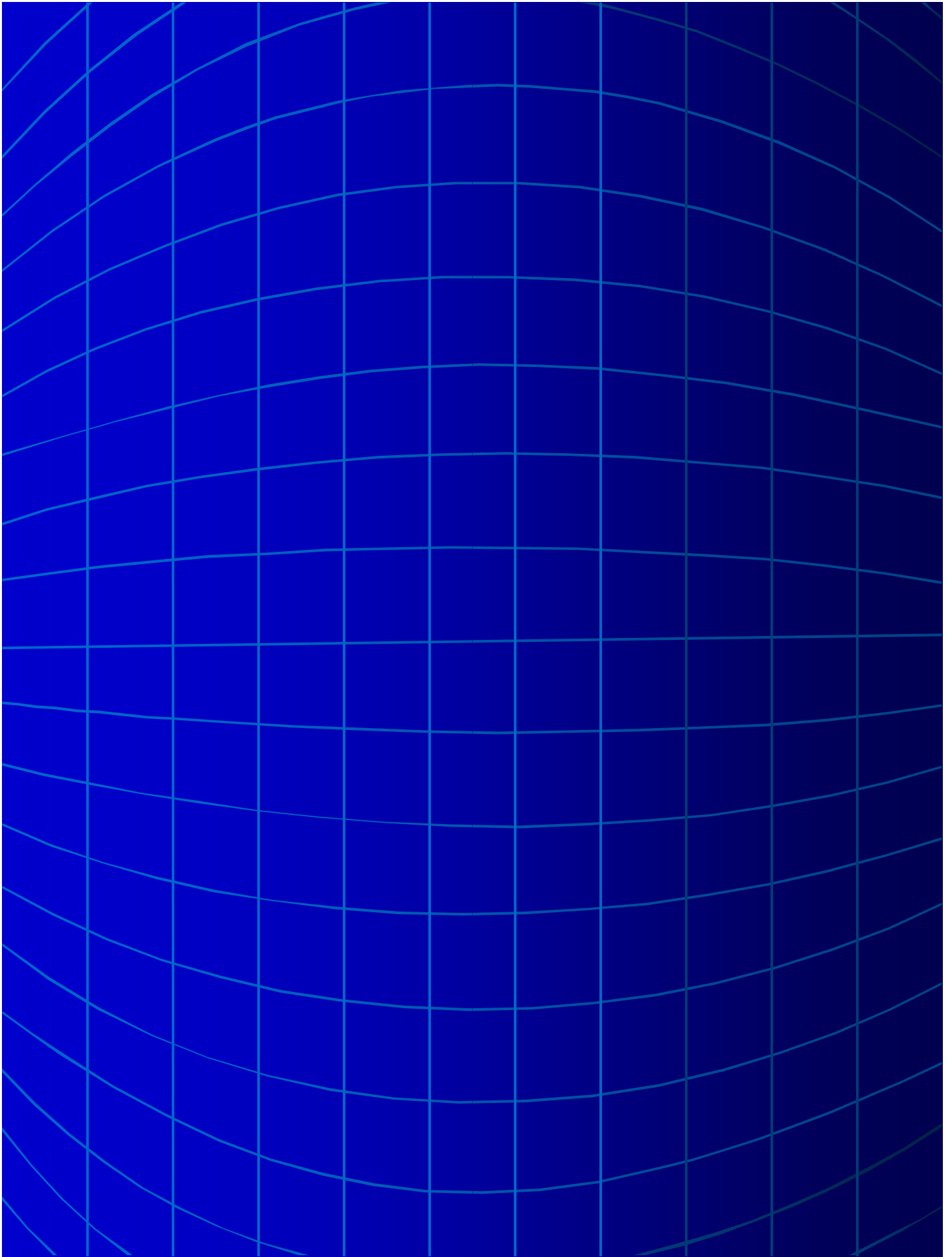
G A C T A A C T T A T C T C C G A C A T G A C T C A G G A T A T G A A G T T C A T C A A A A A T T G G T A C G T A A A A T T A A T T T A C C T C T C

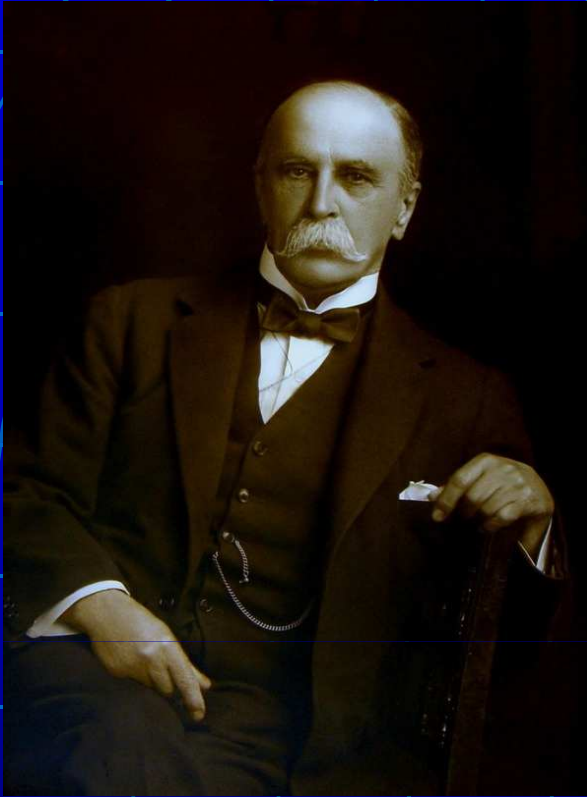
A T C T C A A A A T T A C T G A A G T G A A G A A T C T C A A A A A T T G G T A C G T A A A A T T A A T T T A C C T C T C

6 T 7 A 8 C 9 T 10 A 11 T 12 C 13 G 14 A 15 T 16 C 17 T 18 T

655 660 665 670 675 680 685 688

Exon 16





William Osler (1849-1919)

If there were no individual variability, medicine
would have been science not an art.

Sir William Osler

