THE GENEVA ASSOCIATION

Keynote speech

J. Craig Venter
Co-Founder, Executive Chairman and Head of Scientific Strategy Human Longevity Inc.

HUMAN LONGEVITY, INC.™

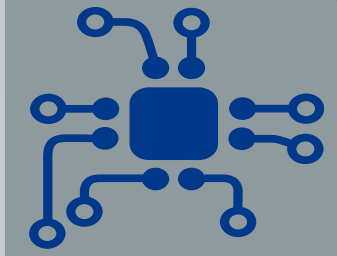
Your Health Intelligence Partner

Reduced Sequencing Costs

The cost of sequencing a full human genome has dropped from $100M in 2001 to ~$1000 in 2014[1]

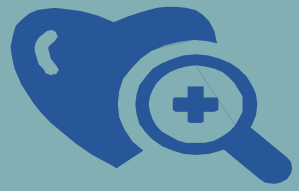
Computation Power

Per law, on average, Moore's price per unit of computing is halved every 24 months[2]



Machine Learning

Machine learning becomes mainstream due to quality breakthroughs and the exponential increase in data availability



Value-based Care

The health system is moving to a model more focused on value.
The health care system about to be disrupted.

J. Craig Venter, PhD, Co-Founder, Executive Chairman, Head of Scientific Strategy

- One of the 21st century leading scientists for contributions to genomic research. Also serves as Founder, Chairman and CEO of J. Craig Venter Institute and Co-Founder and Executive Chairman of Synthetic Genomics, Inc.

Cindy Collins, MBA, Chief Executive Officer

- Cindy brings more than 35 years of experience in leading global teams in diagnostic, life sciences and biopharma businesses. She has held executive roles at GE Healthcare, GenVec, Beckman Coulter, Baxter Healthcare and Abbott Laboratories.

Saturnino (Nino) Fanlo, Chief Financial Officer

- Nino joins HLI in June from Sofi, bringing decades of financial services acumen an strategic leadership to HLI.

Dale Gordon, Chief Commercial Officer

- Deep background in commercial and sales operations across multiple industries. Most recently served as the Commercial GM for GE Healthcare leading the development and execution of the commercial account management strategy. Prior to GE Dale had a long career at Merck Millipore.

Travis Lacey, MBA, Chief Corporate Development Officer

- Extensive background in business development, investment banking and project management playing key roles at GE Healthcare, Robert W. Baird, and Abbott Laboratories.

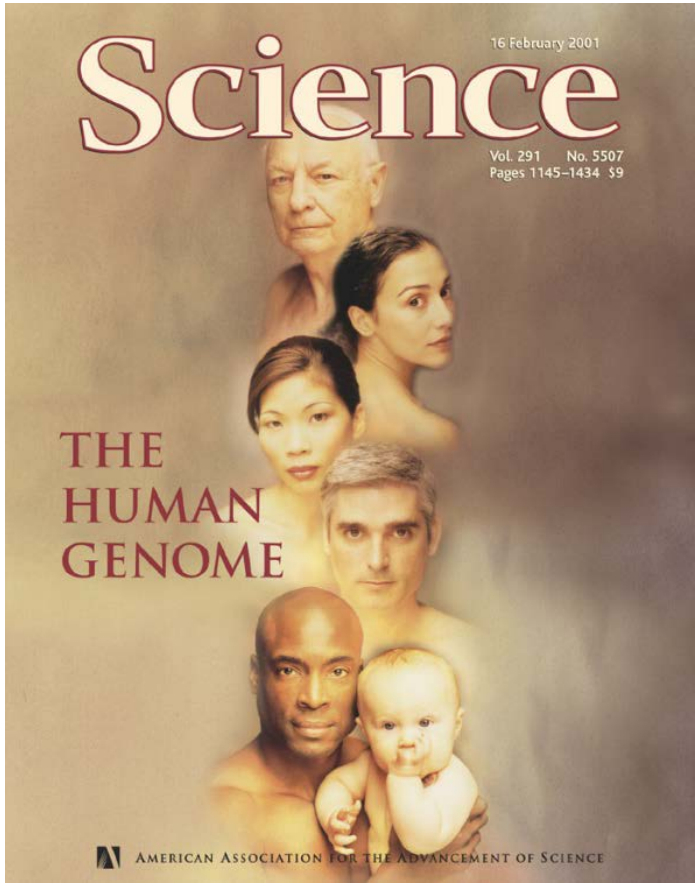
David Heckerman, MD, PhD, Chief Data Scientist

- Joins HLI as a 25-year veteran of Microsoft with an extensive background in machine learning, genomics and cloud computing.

Gary Altman, PhD, Chief Operating Officer

- Tenured strategy and operations executive with experience across several verticals and with significant depth in biotech and start up ventures. Gary held previous roles as CEO, COO and GM at several biotechs including Beckman Coulter and Sequoia Pharmaceuticals.

A DECADE LONG JOURNEY OF IMPROVING HUMAN HEALTH



OPEN ACCESS Freely available online PLoS BIOLOGY

The Diploid Genome Sequence of an Individual Human

Samuel Levy[1*], Granger Sutton[1], Pauline C. Ng[1], Lars Feuk[2], Aaron L. Halpern[1], Brian P. Walenz[1], Nelson Axelrod[1], Jiaqi Huang[1], Ewen F. Kirkness[1], Gennady Denisov[1], Yuan Lin[1], Jeffrey R. MacDonald[2], Andy Wing Chun Pang[2], Mary Shago[2], Timothy B. Stockwell[1], Alexia Tsiamouri[1], Vineet Bafna[3], Vikas Bansal[3], Saul A. Kravitz[1], Dana A. Busam[1], Karen Y. Beeson[1], Tina C. McIntosh[1], Karin A. Remington[1], Josep F. Abril[4], John Gill[1], Jon Borman[1], Yu-Hui Rogers[1], Marvin E. Frazier[1], Stephen W. Scherer[2], Robert L. Strausberg[1], J. Craig Venter[1]

1 J. Craig Venter Institute, Rockville, Maryland, United States of America, 2 Program in Genetics and Genomic Biology, The Hospital for Sick Children, and Molecular and Medical Genetics, University of Toronto, Toronto, Ontario, Canada, 3 Department of Computer Science and Engineering, University of California San Diego, La Jolla, California, United States of America, 4 Genetics Department, Facultat de Biologia, Universitat de Barcelona, Barcelona, Spain

Presented here is a genome sequence of an individual human. It was produced from ~32 million random DNA fragments, sequenced by Sanger dideoxy technology and assembled into 4,528 scaffolds, comprising 2,810 million bases (Mb) of contiguous sequence with approximately 7.5-fold coverage for any given region. We developed a modified version of the Celera assembler to facilitate the identification and comparison of alternate alleles within this individual diploid genome. Comparison of this genome and the National Center for Biotechnology Information human reference assembly revealed more than 4.1 million DNA variants, encompassing 12.3 Mb. These variants (of which 1,288,319 were novel) included 3,213,401 single nucleotide polymorphisms (SNPs), 53,823 block substitutions (2–206 bp), 292,102 heterozygous insertion/deletion events (indels)(1–571 bp), 559,473 homozygous indels (1–82,711 bp), 90 inversions, as well as numerous segmental duplications and copy number variation regions. Non-SNP DNA variation accounts for 22% of all events identified in the donor, however they involve 74% of all variant bases. This suggests an important role for non-SNP genetic alterations in defining the diploid genome structure. Moreover, 44% of genes were heterozygous for one or more variants. Using a novel haplotype assembly strategy, we were able to span 1.5 Gb of genome sequence in segments >200 kb, providing further precision to the diploid nature of the genome. These data depict a definitive molecular portrait of a diploid human genome that provides a starting point for future genome comparisons and enables an era of individualized genomic information.

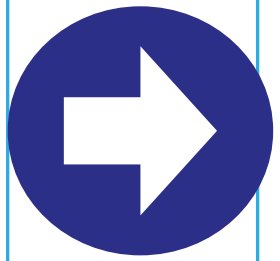
J. Craig Venter INSTITUTE

PLoS Biology 2007 5:e254

HLI'S GOAL IS TO CHANGE THE PRACTICE OF MEDICINE

HEALTHCARE TODAY

- REACTIVE
- DISEASE MANAGEMENT
- GENERALIZED
- COSTLY



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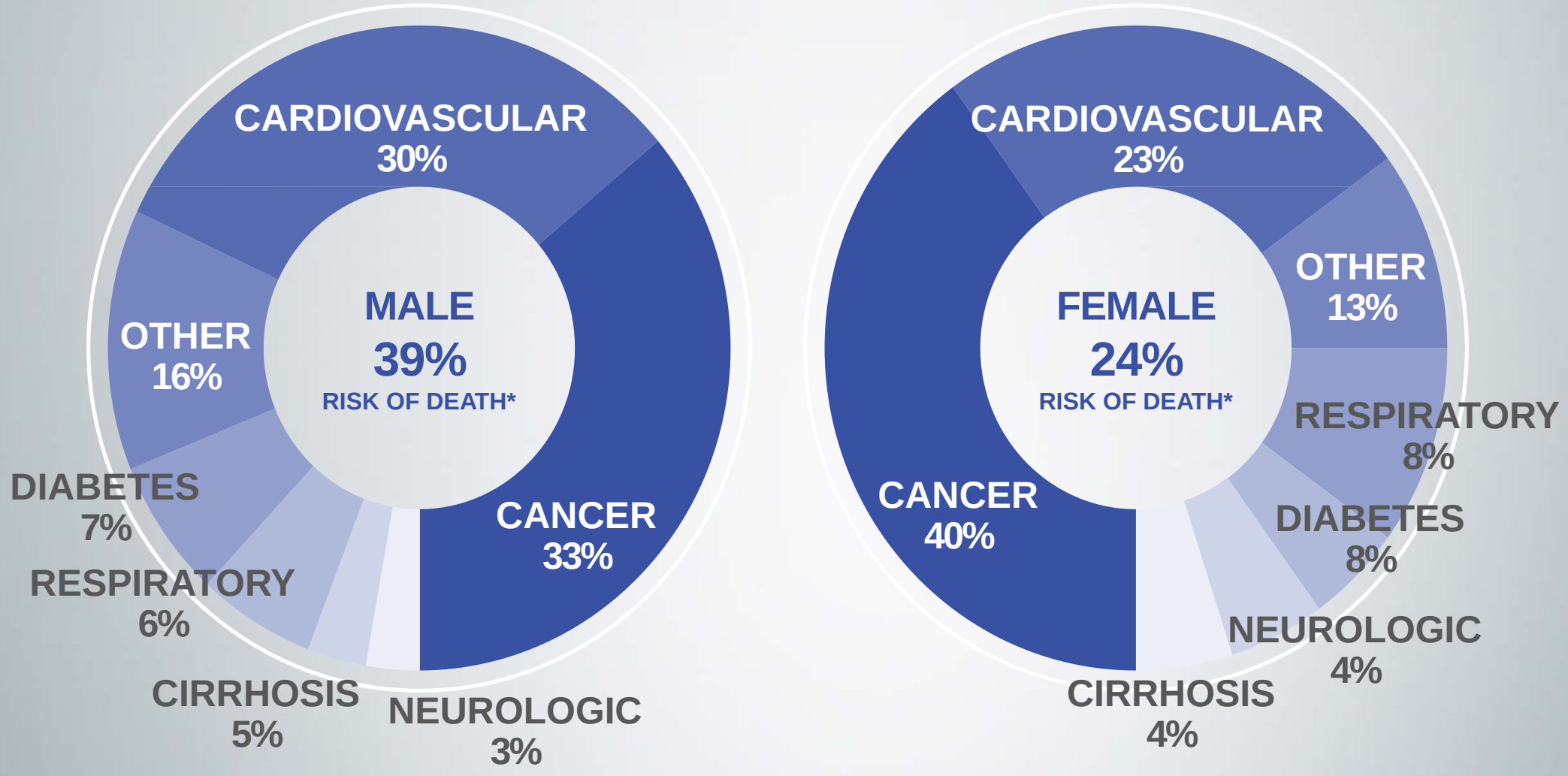
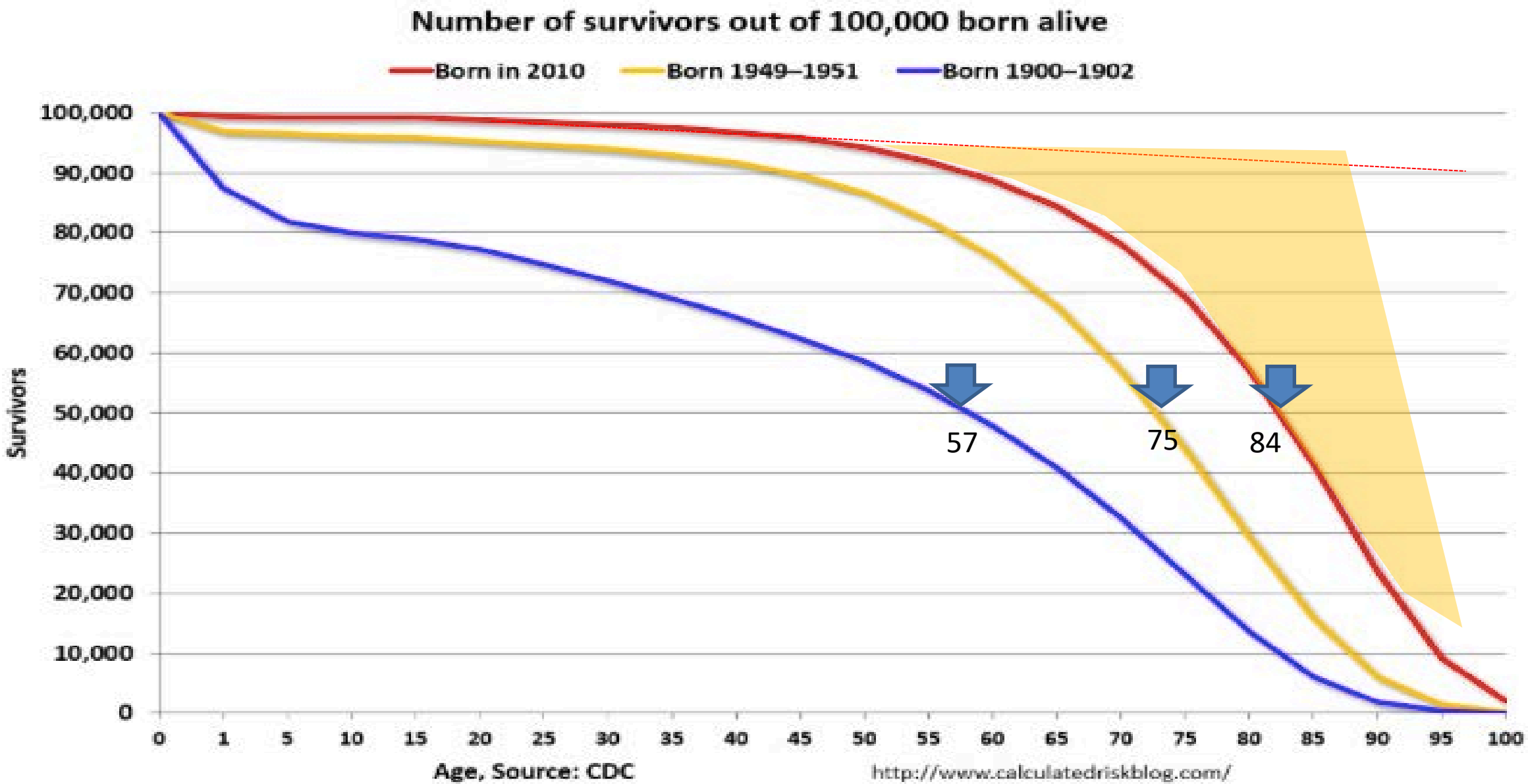
- PROACTIVE
- PREVENTATIVE
- PERSONALIZED
- PREDICTIVE

Age-Related Chronic Diseases are Leading Causes of Pre-Mature Mortality in US Adults, 50-74 years



* Ages 50 – 74, 2015 in USA; Adapted from Institute of Health Metrics and Evaluation, University of Washington. http://www.healthdata.org/results/data-visualizations

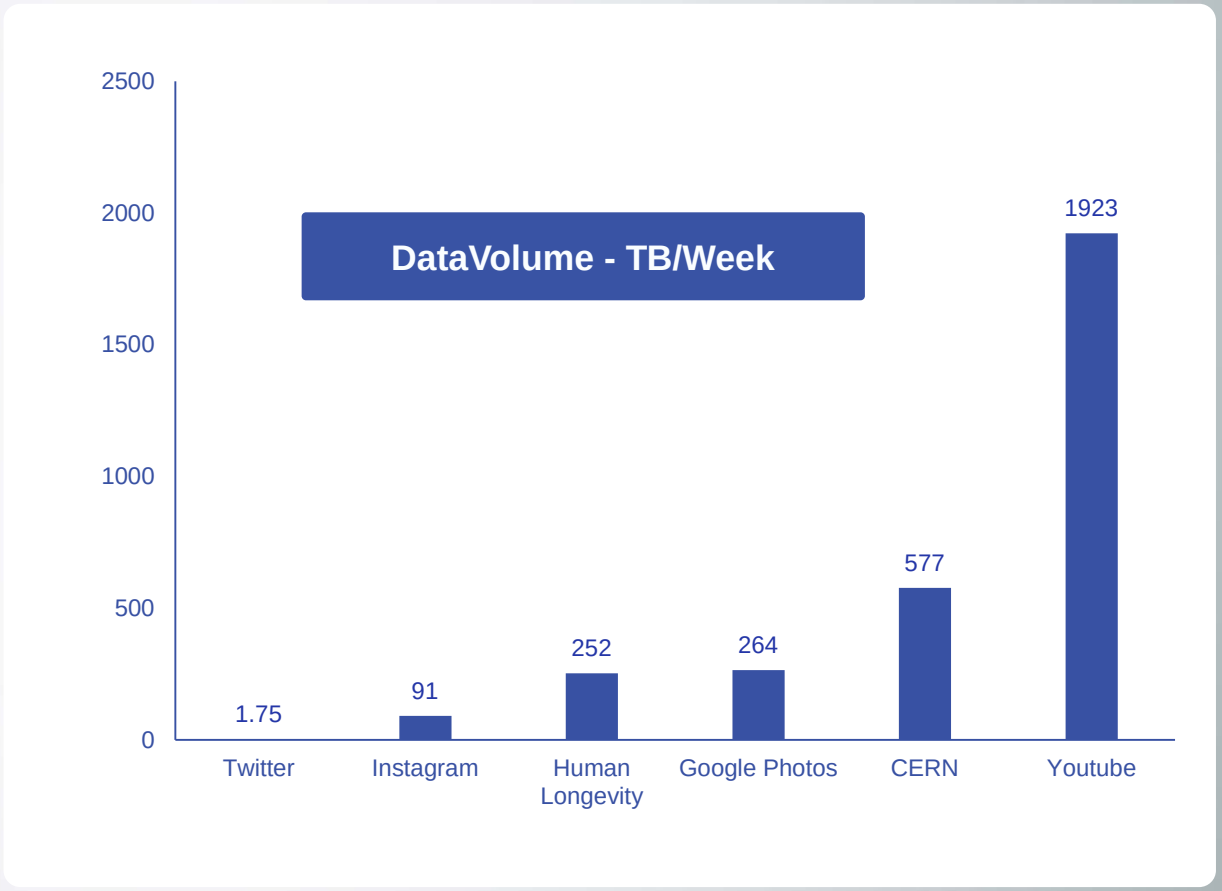
Genome burden and aging




HUMAN LONGEVITY HAS SEQUENCED OVER
41,686 FULL HUMAN GENOMES TO DATE
OVER 4.9 PETABYTES OF BASEPAIRS
SEQUENCED
HiSeqX
OBI-WAN
CORUSCANT

HLI is at the Forefront of Big Data

- In the top 1% of all AWS customers
  - The only customer to ever hit 1% in under 2 years
- Close to 1,000,000 EC2 (elastic cloud compute) instance hours used per month
  - 11 years of core hours used per day to just to analyze raw sequence data
- 8PB of data per year and growing
- Over 20PB of genomics data stored today
  - 1 Million WGS will require nearly 1 Exabyte of data



UNPARALLED SEQUENCING QUALITY AND PERFORMANCE

HUMAN LONGEVITY, INC.

PNAS

Deep sequencing of 10,000 human genomes

Amalio Telenti[a,b,1], Levi C. T. Pierce[a,c,1], William H. Biggs[a,1], Julia di Iulio[a,b], Emily H. M. Wong[a], Martin M. Fabani[a], Ewen F. Kirkness[a], Ahmed Moustafa[a], Naisha Shah[a], Chao Xie[d], Suzanne C. Brewerton[d], Nadeem Bulsara[a], Chad Garner[a], Gary Metzker[a], Efren Sandoval[a], Brad A. Perkins[a], Franz J. Och[a,c], Yaron Turpaz[a,d], and J. Craig Venter[a,b,2]

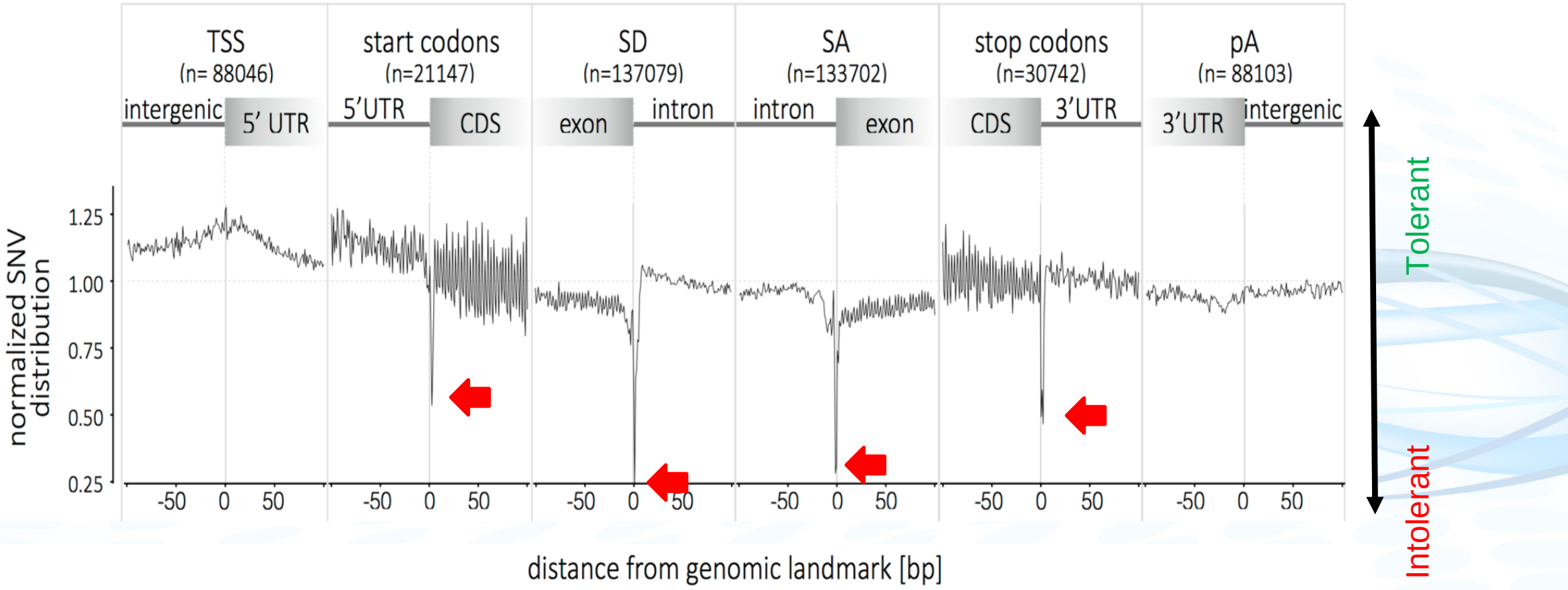
Quality Metrics:
*False discovery = **0.0008***
*Precision = **0.999***
*Recall = **0.994***

*This work extended the **high confidence sequence regions from 70% to 84%** of the genome.*

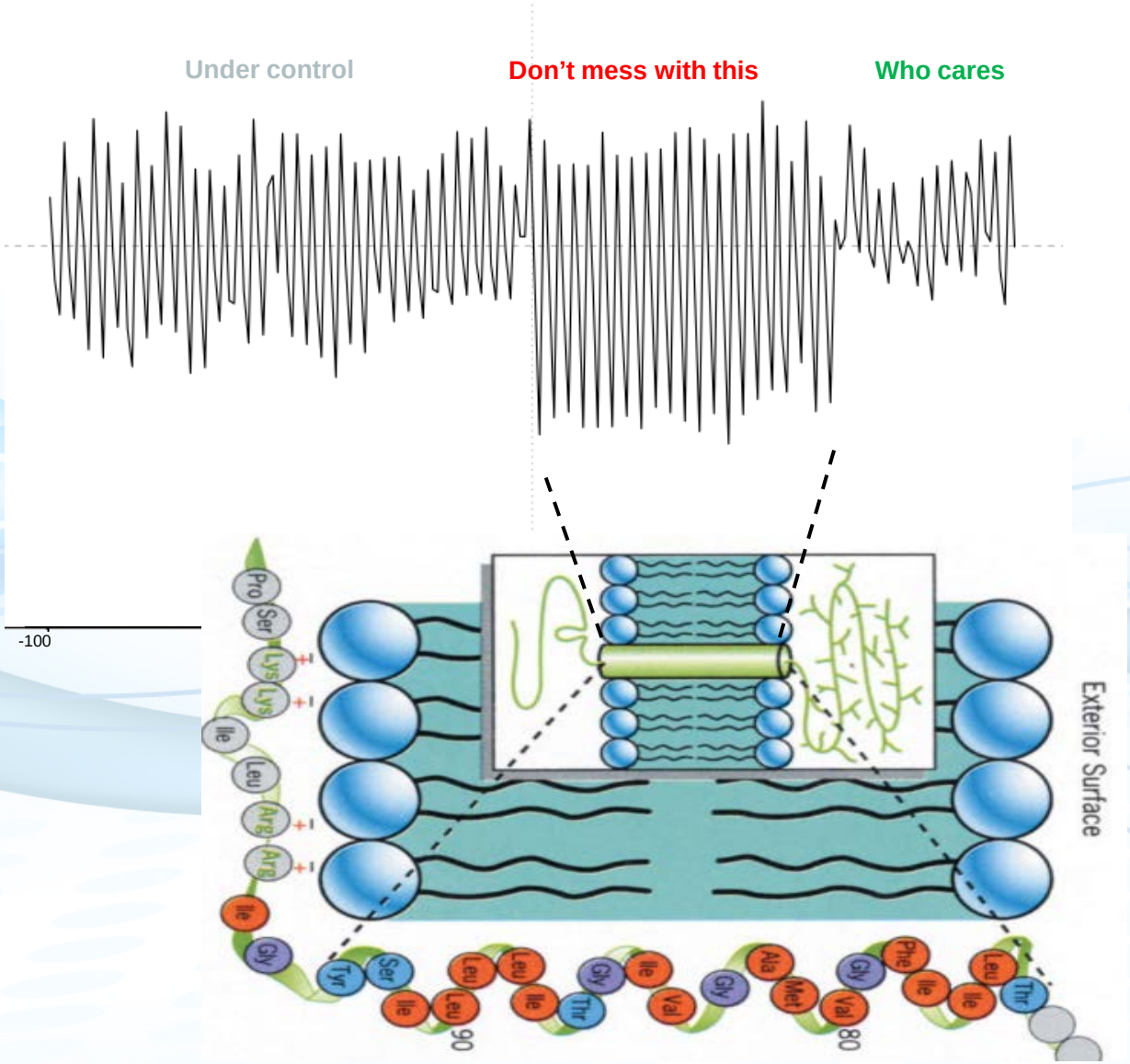
Our quality criteria are now adopted by NIH as requirements for genome center contracts.

*Approximate **92%** of high confidence coverage of exomic regions and **96%** of sites that are associated with **pathogenic variants** in the genome.*

1 billion datapoints



23,778 Transmembrane Domains



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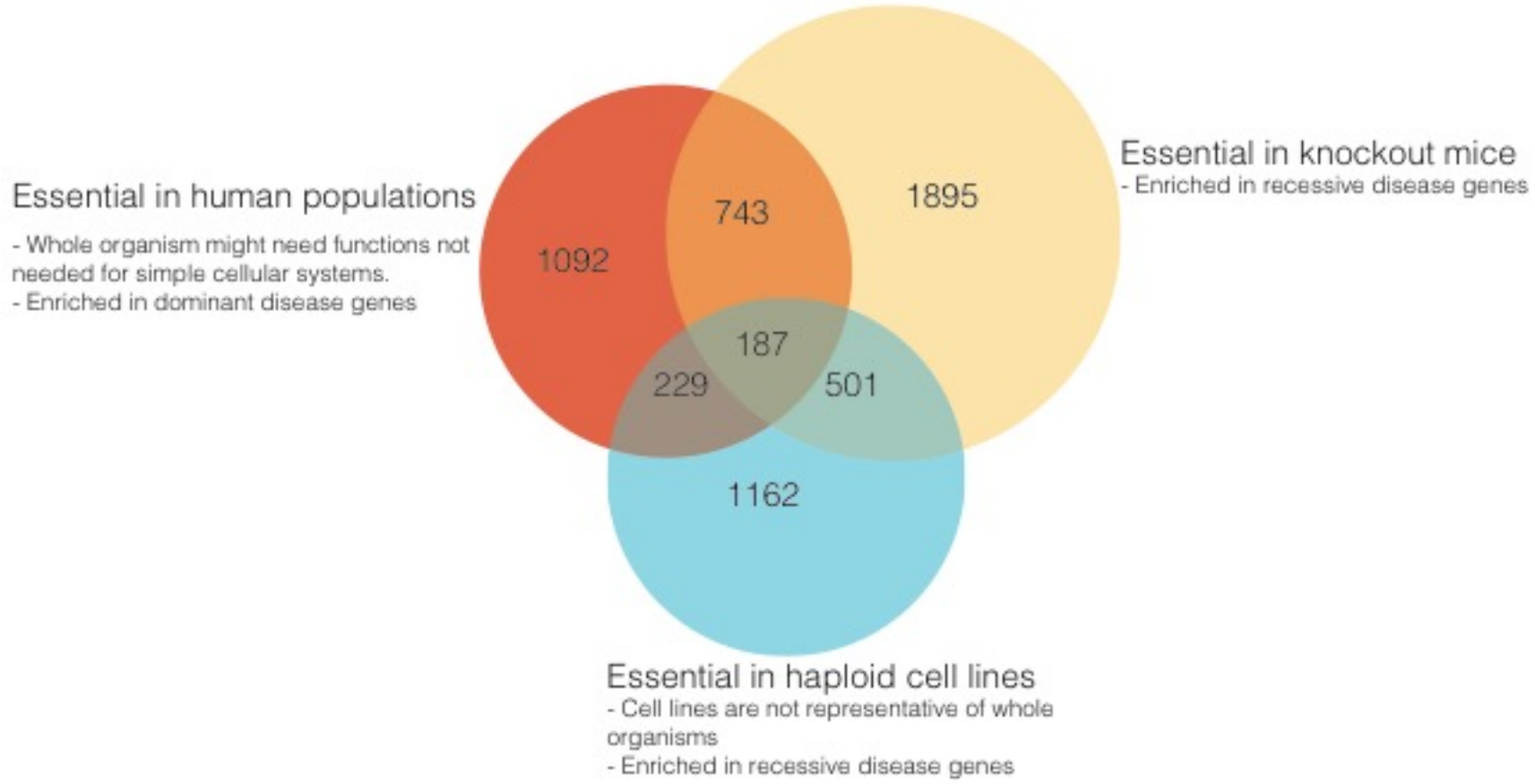
Human Essential Genes

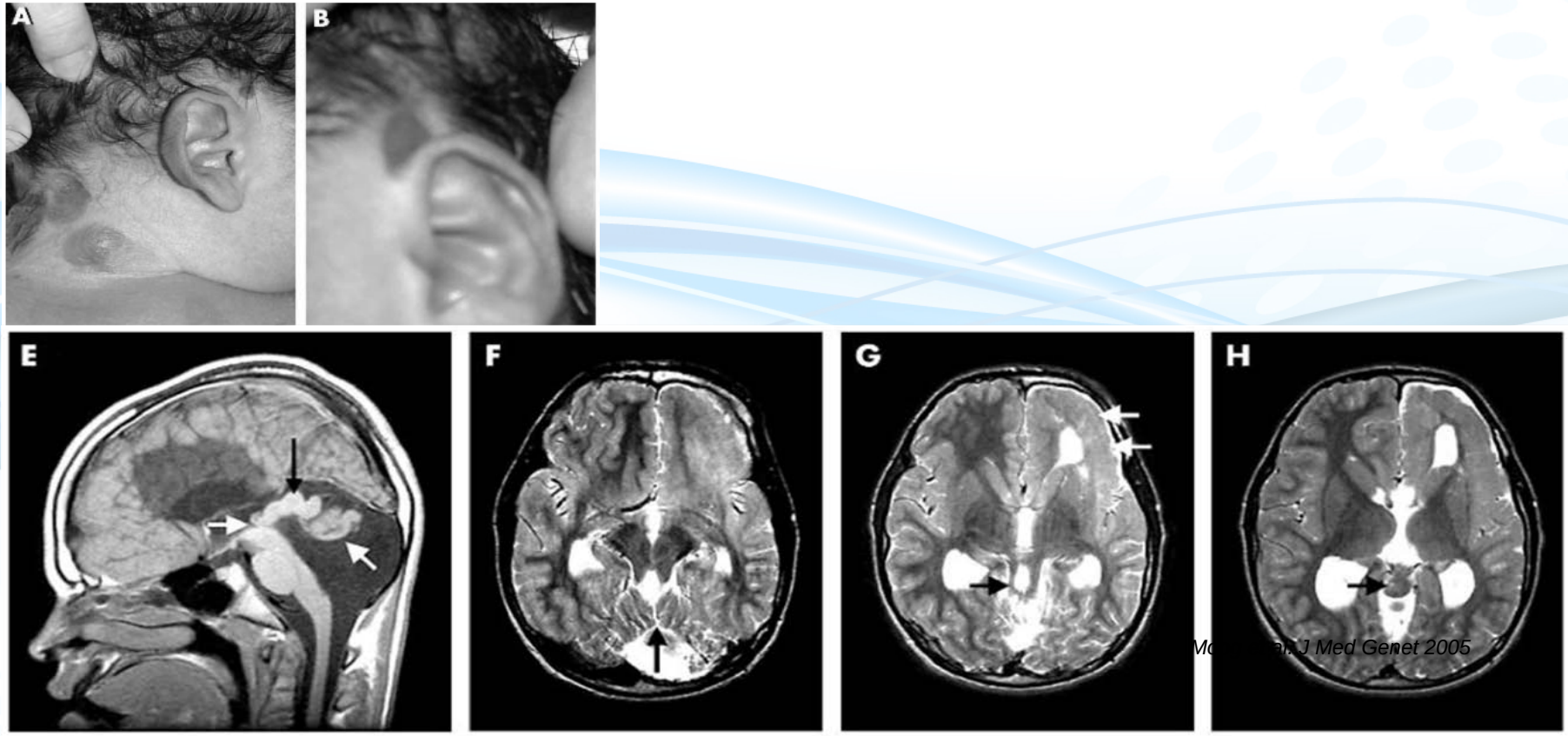


- Essentiality can be estimated from human population studies (HLI), in mice (knockouts), and in cellular systems (CRIPR-Cas9 editing).
- These are different measurements but that converge in a core set of 187 essential genes

Rare Disease Case

Case:

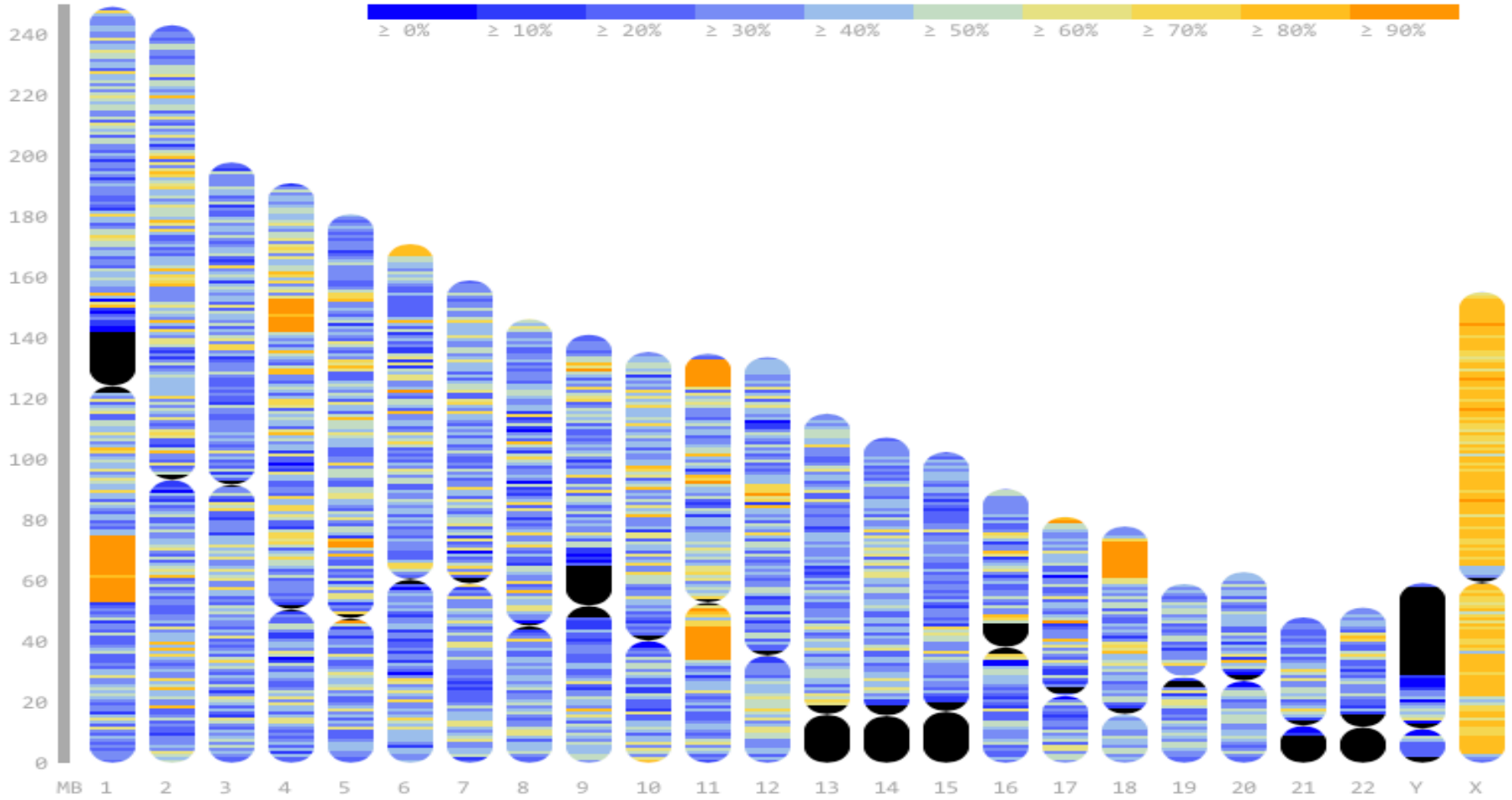
11 yo child presented with Delleman Syndrome and a request to investigate a rare nervous system congenital disorder within 2 weeks

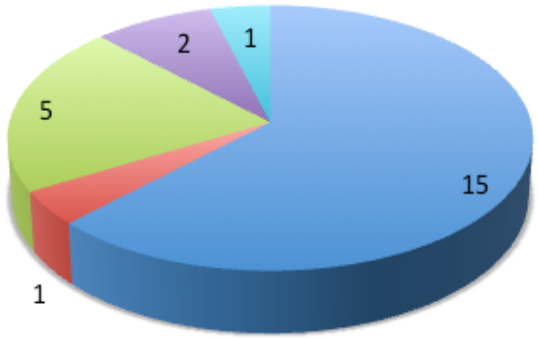


Am J Med Genet 2005

Percentage of variants that are Homozygous

Data is shown within 1MB regions. Black represents regions with fewer than 5 variants per 1MB.





Negative

Neurofibromatosis

Gene associated with brain developmental process/ abnormalities

Gene associated with CNS function

Other syndroms

NF1*

CD28*#
TSPAN10*
GPR161*
THBS2*#
DAB1#

(TBP*)
(CACNA1A*)

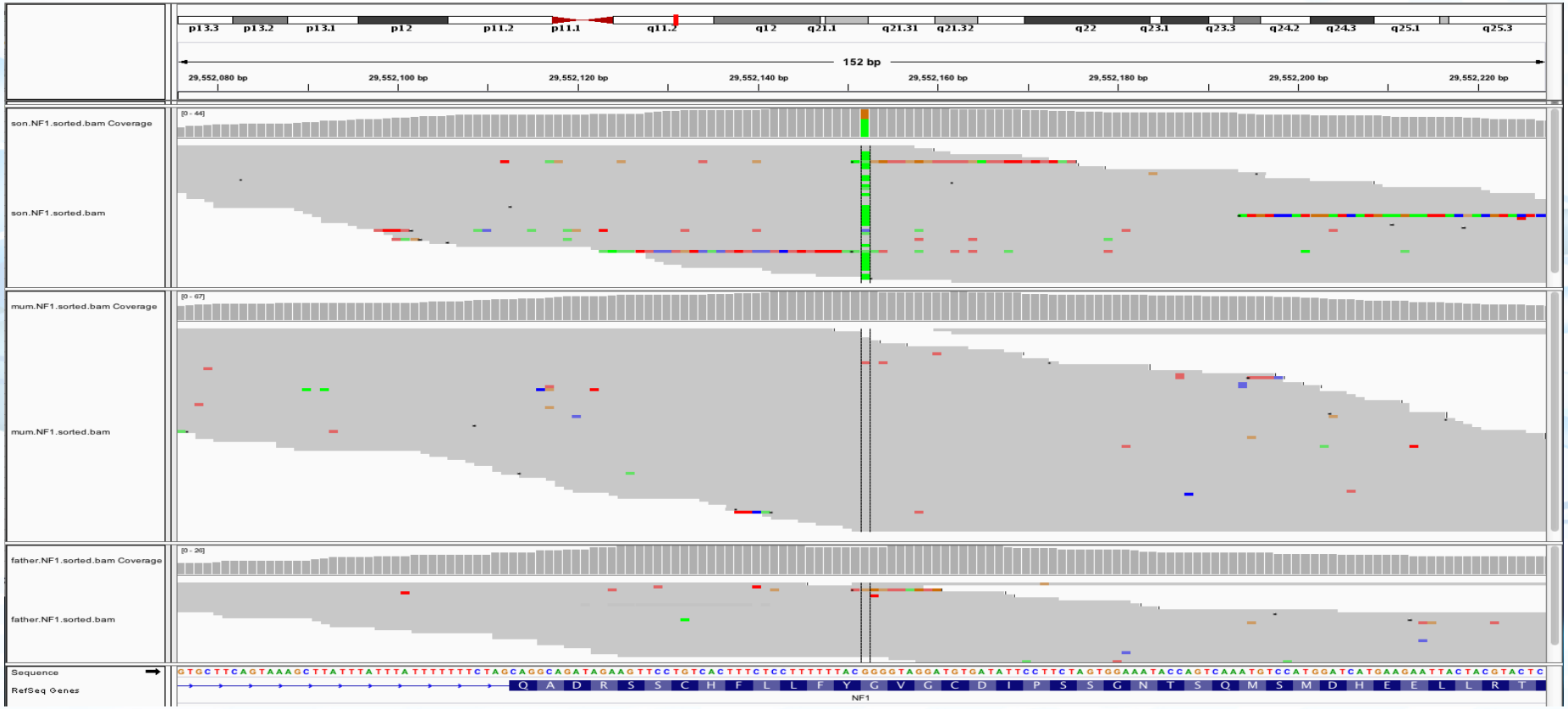
NEB*

Candidate Gene List

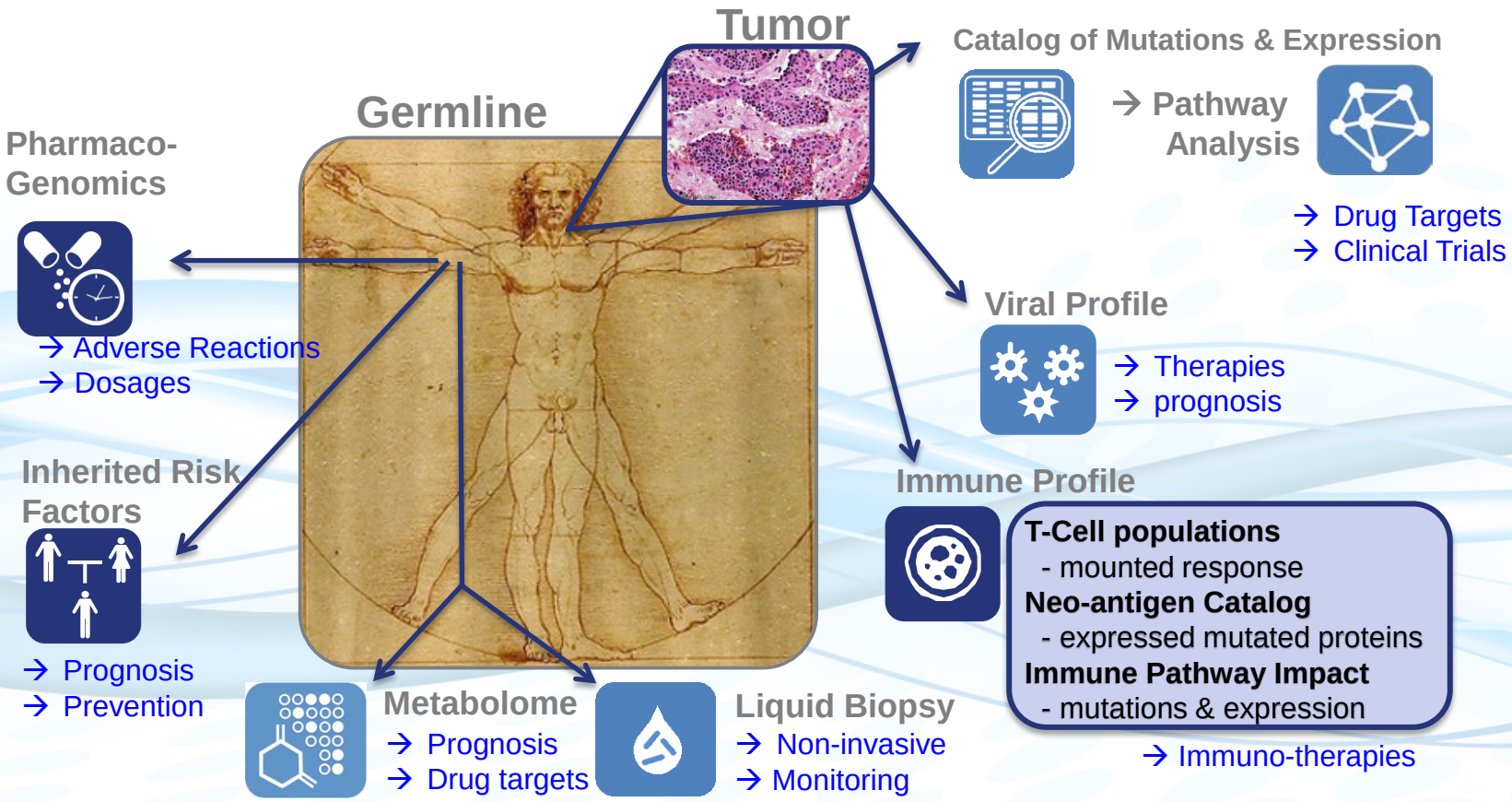
**=coding#mouse KO*

De novo mutation in NF 1 gene identified

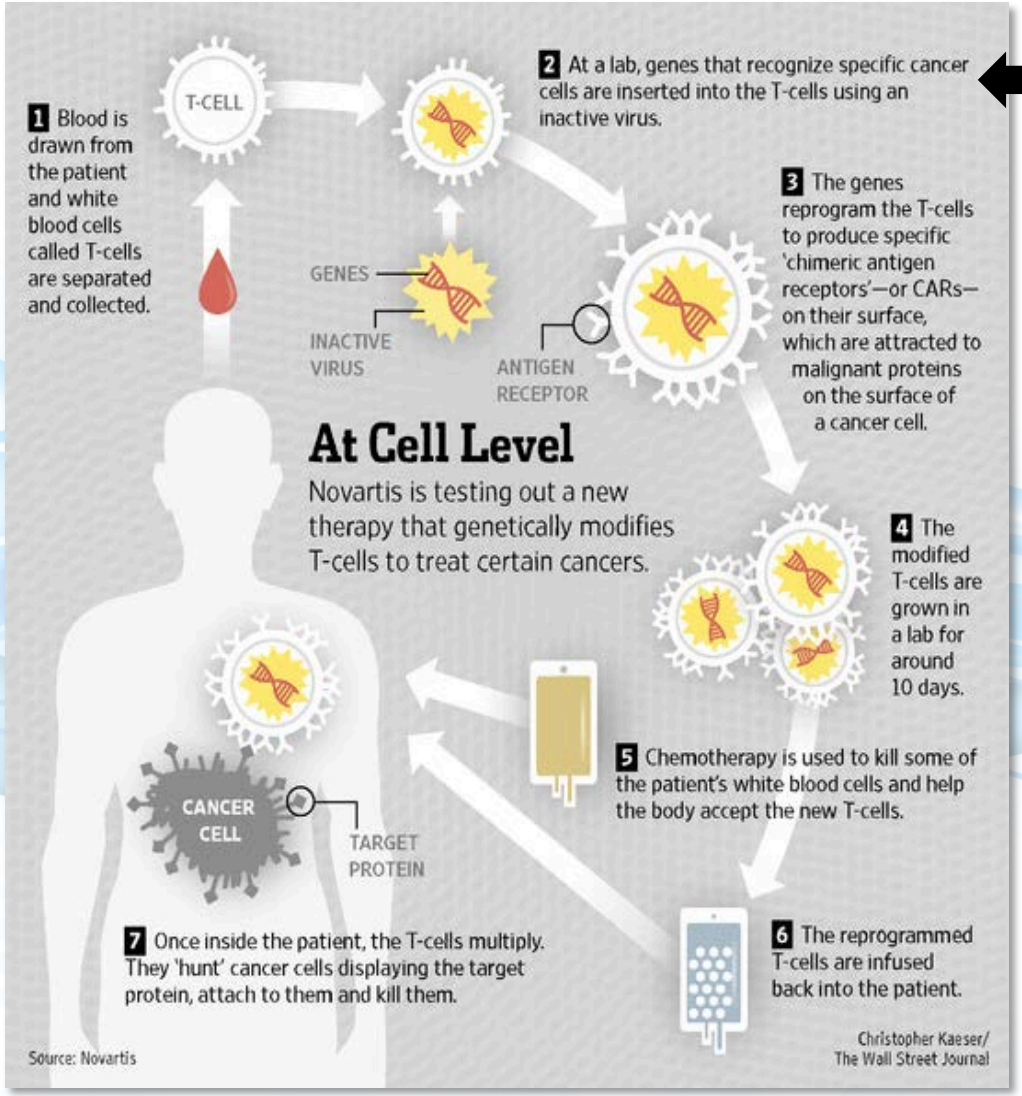
- G ➔A mutation at chr17:29552152 - present only in son (heterozygote)
- Mutation creates a novel splice acceptor site, leading to skipping of the first 41 bp of exon 12b. This variant has been observed patients with neurofibromatosis (autosomal dominant)



HLI COMPREHENSIVE CANCER ANALYSIS GOAL: IDENTIFY BIOMARKERS THAT INFORM THERAPY



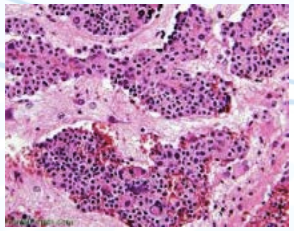
Case study: potential to move from tumor to personalized vaccine



INPUT TARGETS FOR IMMUNE ATTACK (NEOANTIGENS)

315 genes with mutated protein

WHOLE GENOME SEQUENCING (WGS)



TUMOR

HEALTH NUCLEUS

Health Nucleus: PROACTIVE Curative AND Preventive Medicine

PROACTIVE Curative AND Preventive
Identify pathology and risk
Restore health and decrease risk
Promote individual (and family/community) service ethic
Clinical, behavioral, and social interventions

HEALTH NUCLEUS COLLECTED DATA

HUMAN LONGEVITY, INC.

HEALTH DATA COLLECTED BY THE HEALTH NUCLEUS

150 GB
Over an 8 hr day

1 WHOLE BODY
- MRI (musculoskeletal/ lipid analysis)
- MRI (organ specific RSI/diffusion for early cancer detection)
- DEXA Scan
- InBody Biometrics
- Over 70 Laboratory Diagnostic Tests (Blood)
- 3D Forensic Imaging (Avatar)

2 GENOME SEQUENCING
- Whole Genome
- Metabolome
- Microbiome

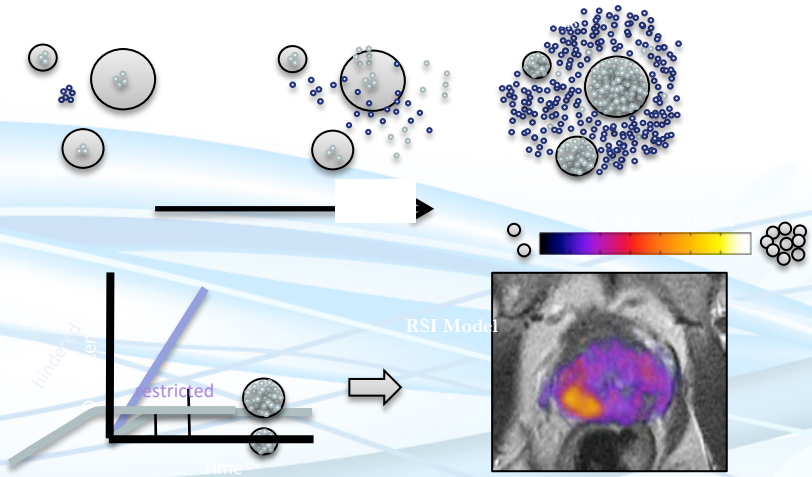
3 BRAIN
- NeuroQuant® Brain MRI
- 3D T2 Brain MRI
- Diffusion MRI
- Neurocognitive Testing
- Quantitative Gait Analysis

4 PULMONOLOGY
- Pulmonary Function Testing

5 CARDIOVASCULAR
- Echocardiography (2D, 3D, 4D)
- ECG
- 2 week Ambulatory Rhythm Testing
- CT calcium score

Advanced DWI: Restriction Spectrum Imaging

(A focus on restricted, isotropic diffusion such as in cells with large N/C ratio)



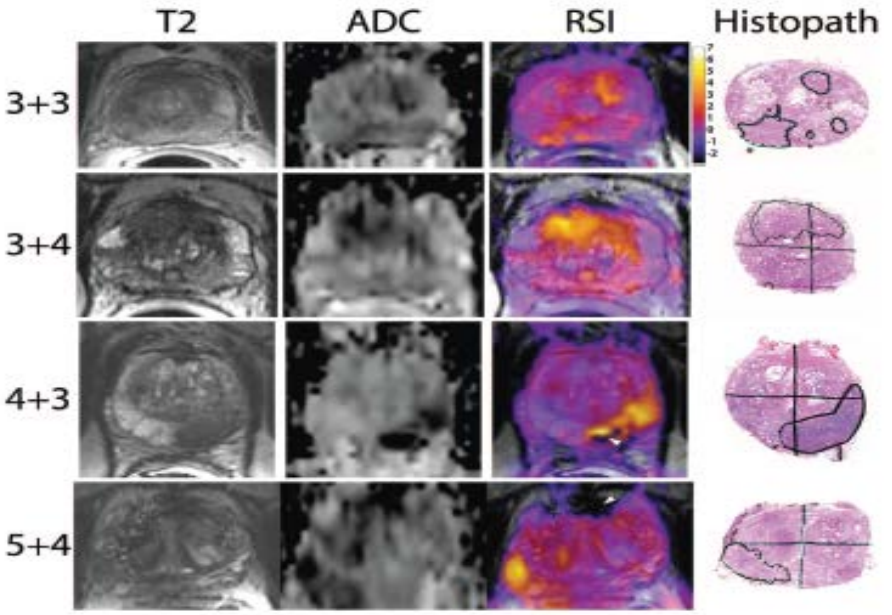
Nathan S. White et al. Cancer Res 2014;74:4638-4652

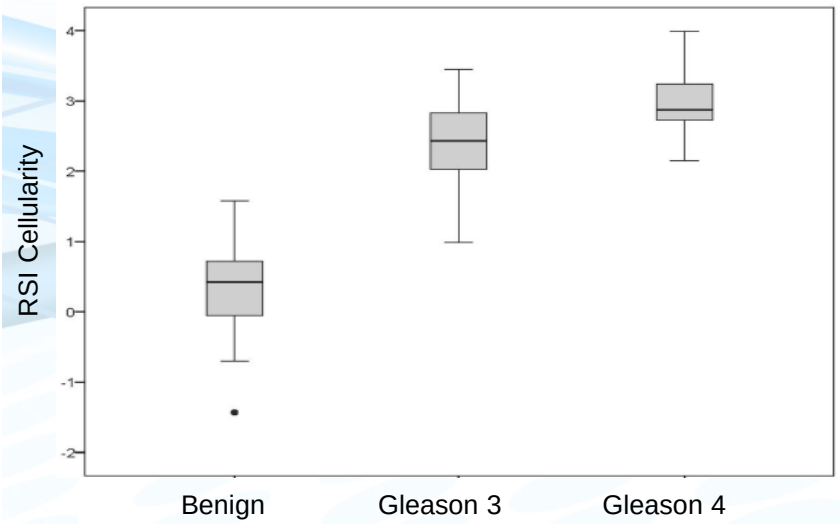
frontiers in ONCOLOGY

ORIGINAL RESEARCH ARTICLE
published: 17 February 2015
doi: 10.3389/fonc.2015.00030

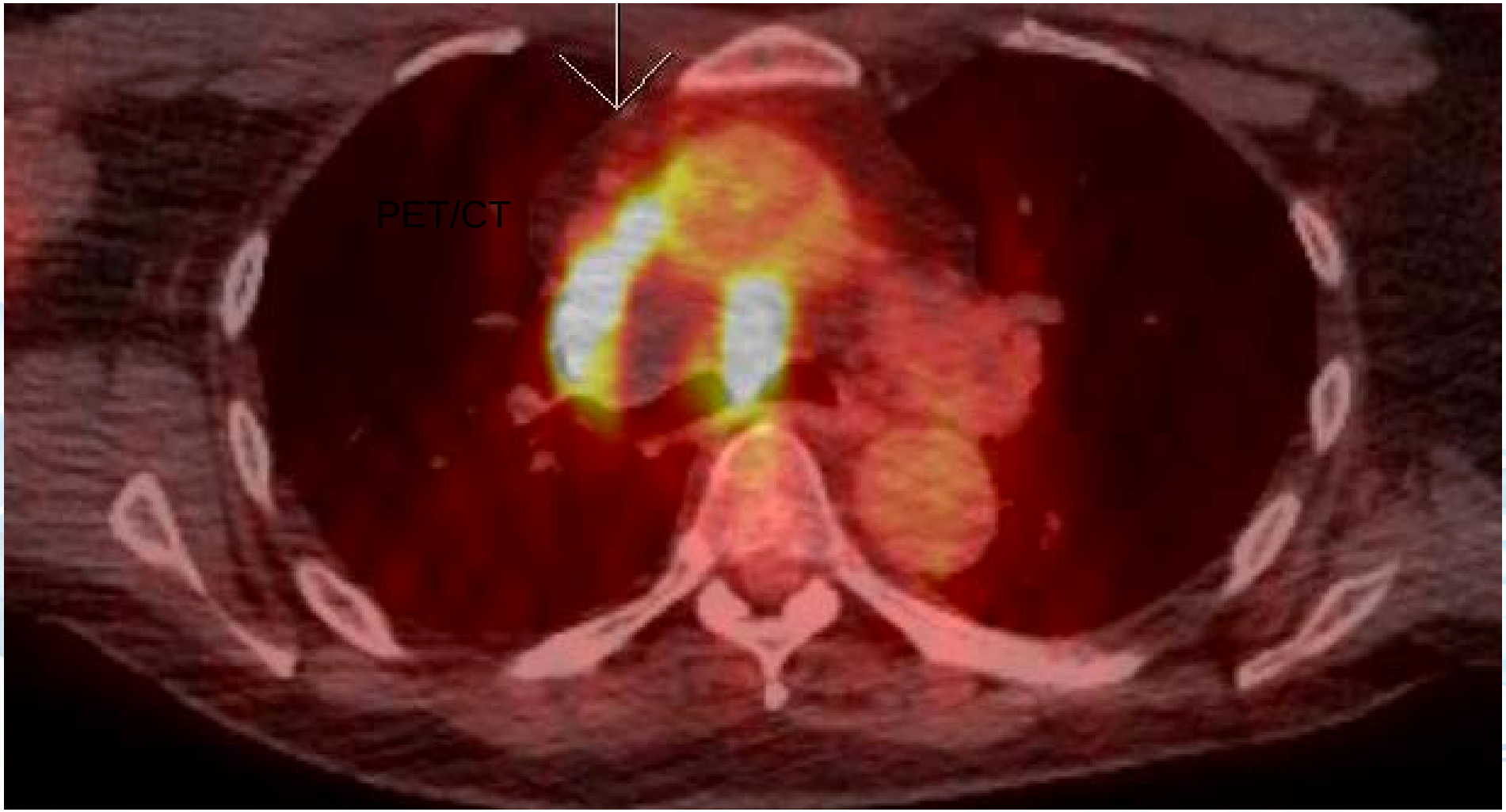
MRI-derived restriction spectrum imaging cellularity index is associated with high grade prostate cancer on radical prostatectomy specimens

Michael A. Liss[1], Nathan S. White[2], J. Kellogg Parsons[1], Natalie M. Schenker-Ahmed[2], Rebecca Rakow-Penner[2], Joshua M. Kuperman[2], Hauke Bartsch[2], Hyung W. Choi[2], Robert F. Mattrey[2], William G. Bradley[2], Ahmed Shabaik[3], Jiaoti Huang[4], Daniel J. A. Margolis[5], Steven S. Raman[5], Leonard S. Marks[6], Christopher J. Kane[1], Robert E. Reiter[6], Anders M. Dale[2,7] and David S. Karow[2]*



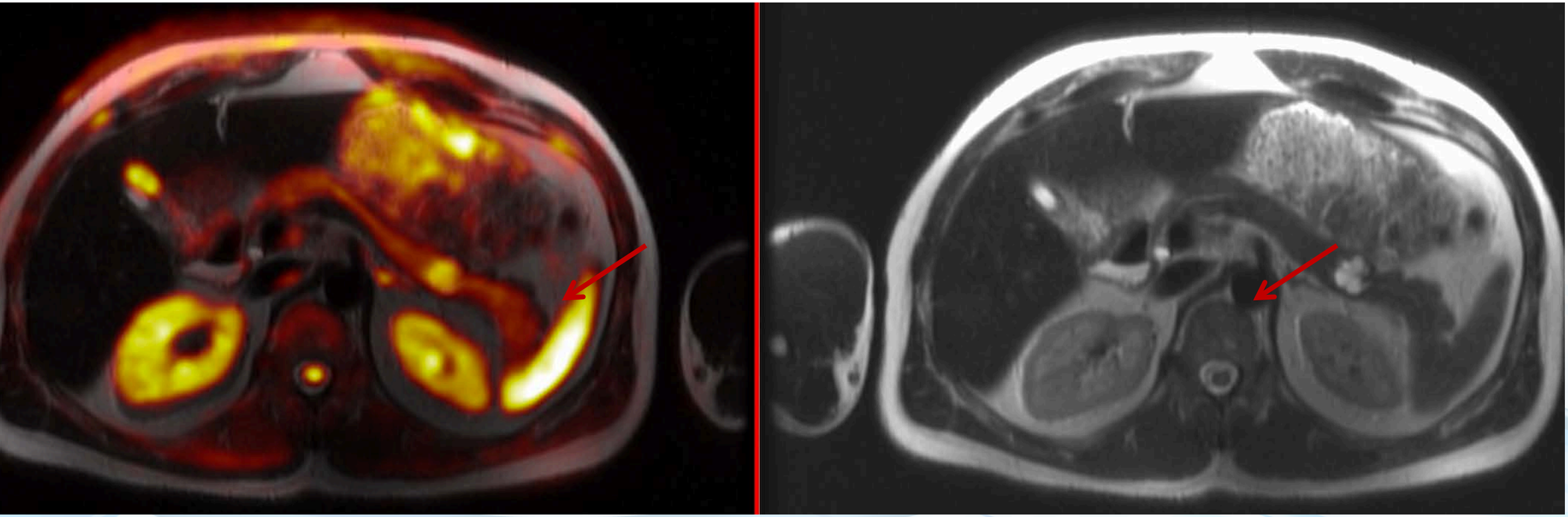


PET/CT: Positive HLI case. 84 yo with newly found mediastinal large B cell lymphoma, early stage. Asymptomatic



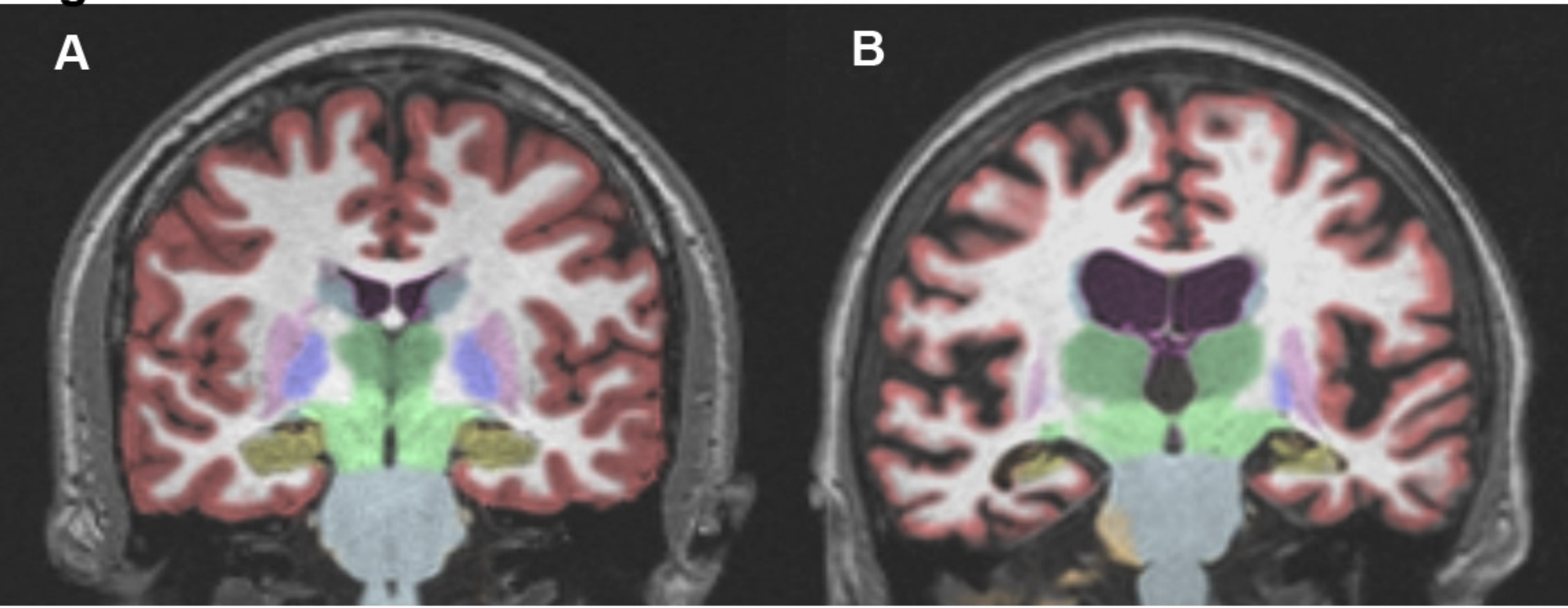
1. **Redemonstration of a right paratracheal mass with peripheral hypermetabolic activity and central necrosis, likely malignant, without evidence of metastatic disease.**

PET/CT and Whole Body MRI are congruent. Early stage with no metastatic disease



T2 images and cellularity images from WB DWI/RSI protocol: 2 cm pancreatic tail mass

Figure 1



NORMAL ALZHEIMER'S DISEASE

Newly Diagnosed Metabolic Disease

42 y/o male, accomplished executive with minimal alcohol use, no known h/o diabetes mellitus; **findings**: elevated BMI: 35 kg/m2 [obese], elevated A1C, liver enzymes, and LDL with very low vitamin D, DEXA scan shows osteopenia and elevated android/gynoid ratio, body MRI reveals liver fat of 35% (normal <4%) c/w nonalcoholic steatohepatitis (NASH)

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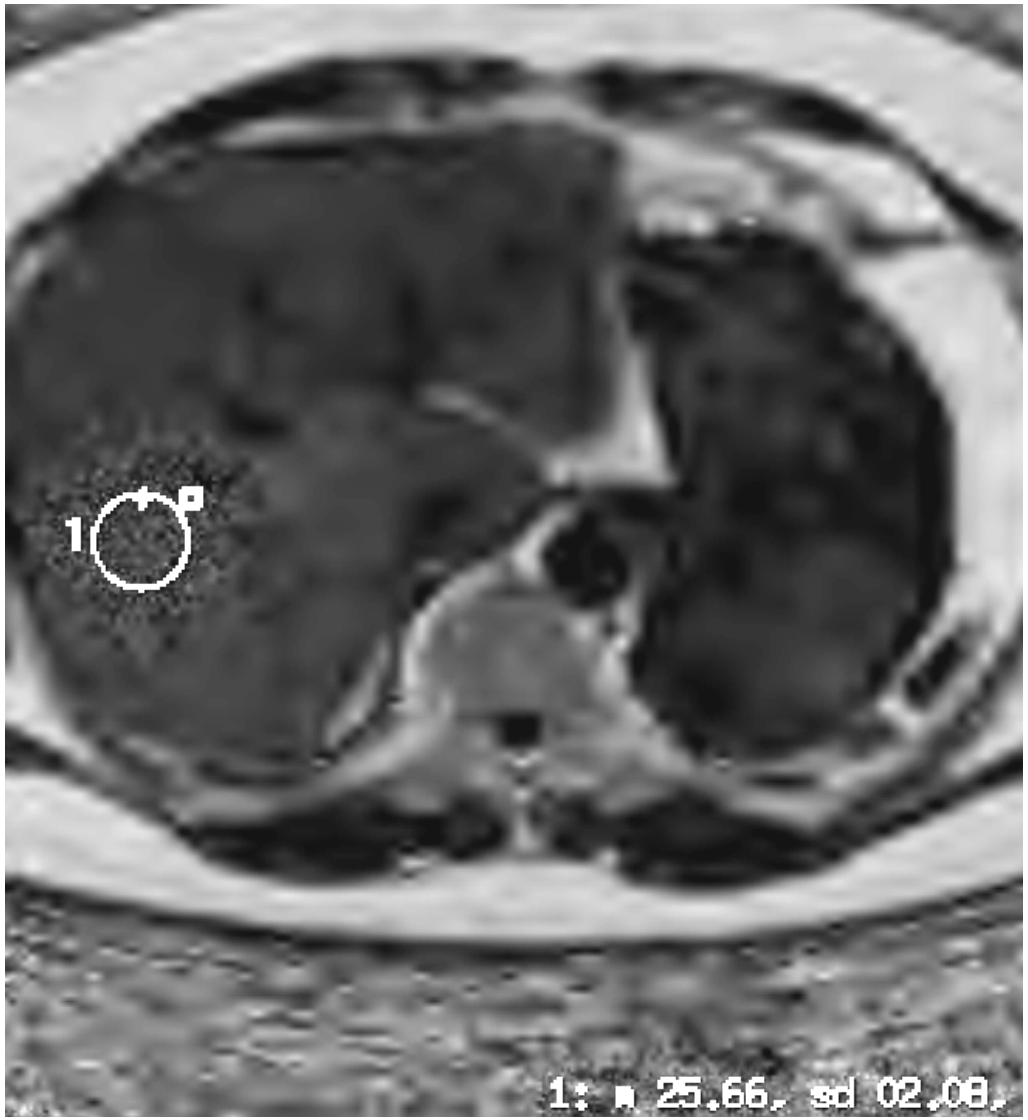
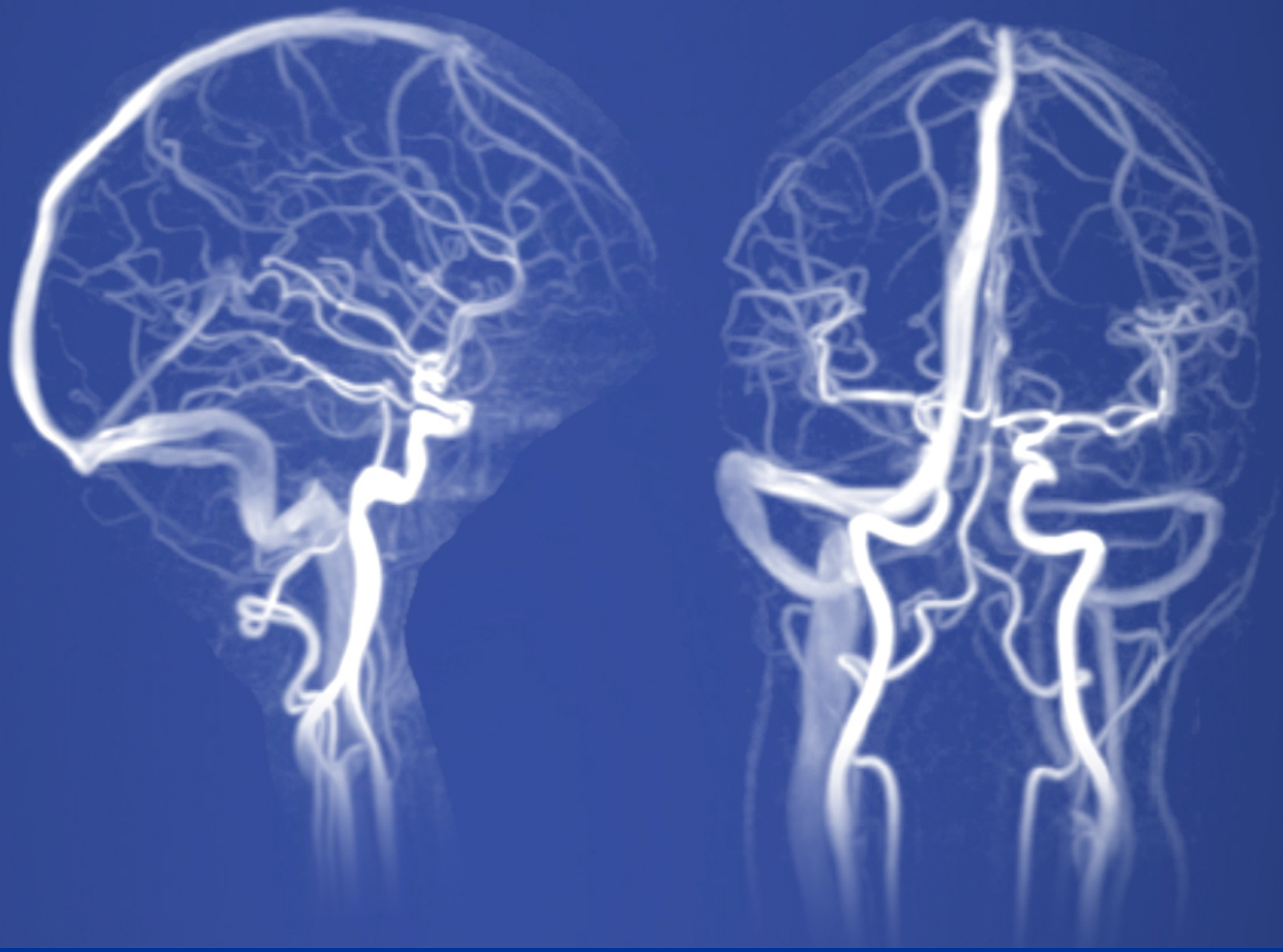


HEALTH NUCLEUS ™

Non-Contrast MR Angiography



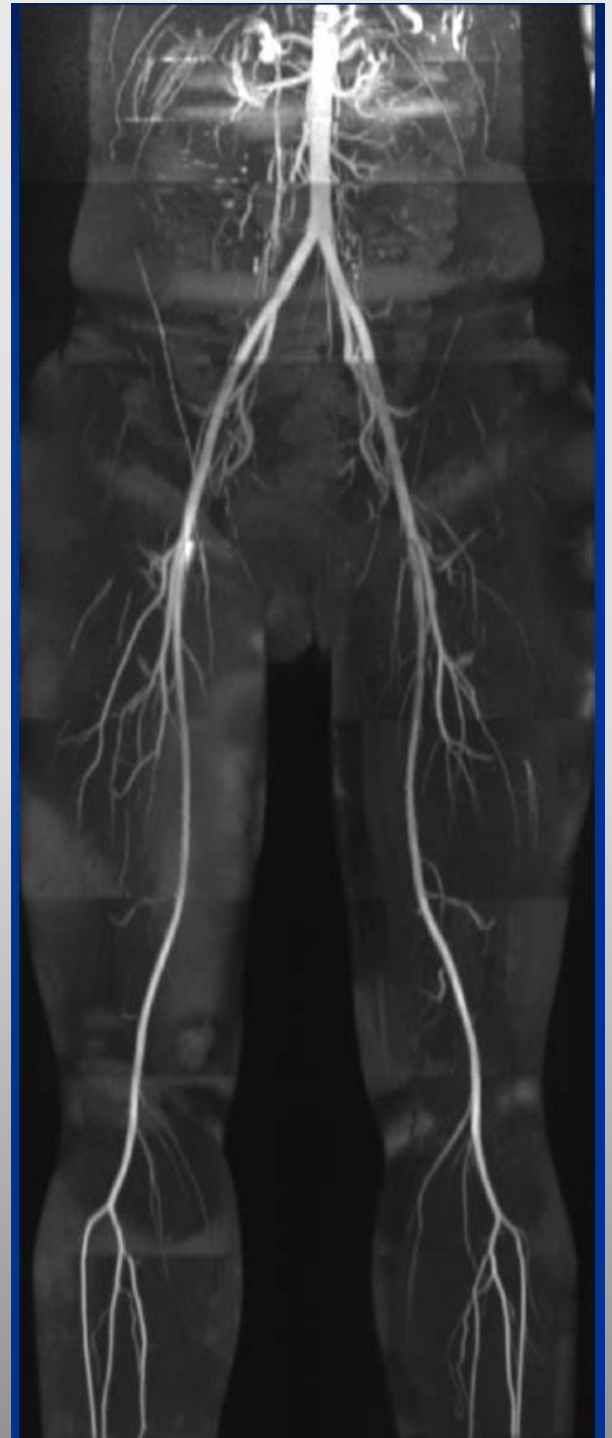
HEALTH NUCLEUS ™

Left Cavernous ICA Brain Aneurysm

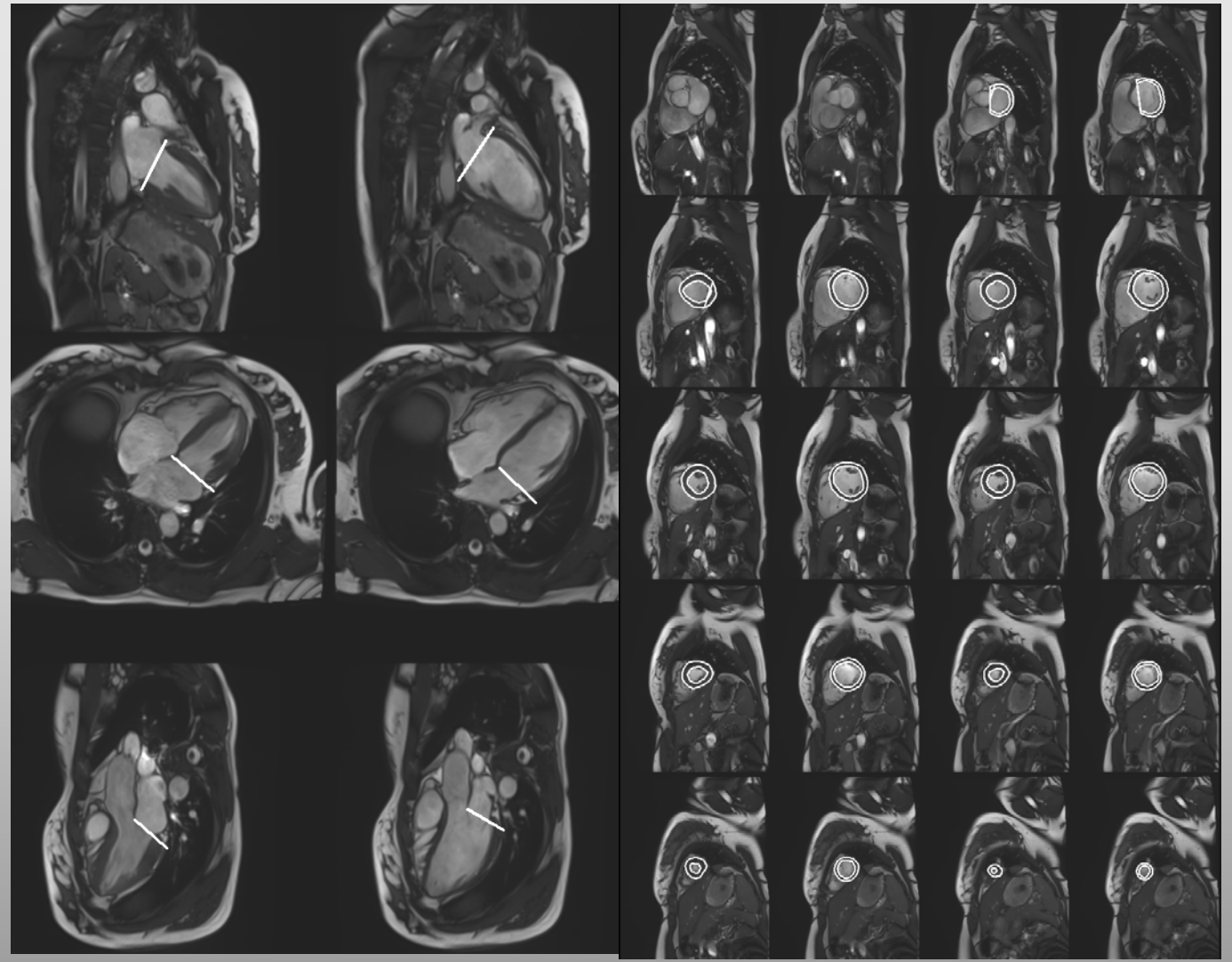
HNx

Changing Healthcare:

Whole Genome Sequencing & WB MRI



15 minute non-contrast cardiac MRI based on compressed sensing: Automated functional output



Automated ROI generation

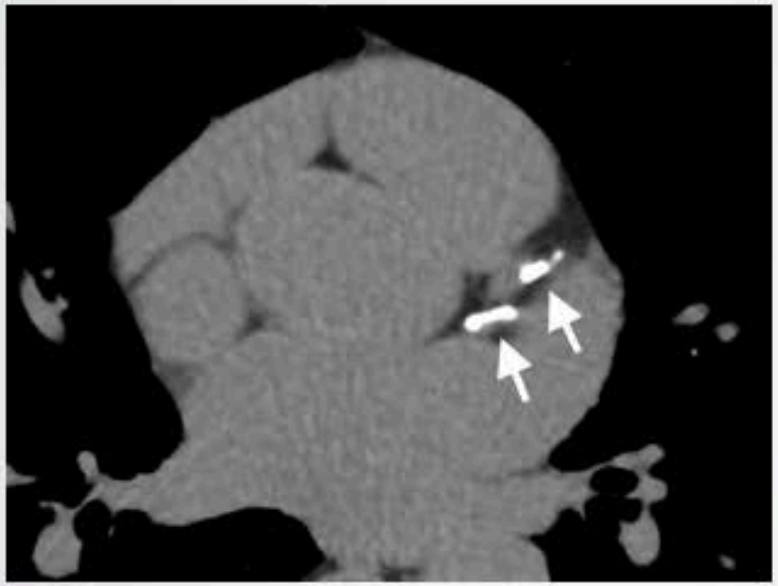
15 minute non-contrast cardiac MRI based on compressed sensing: Automated functional output

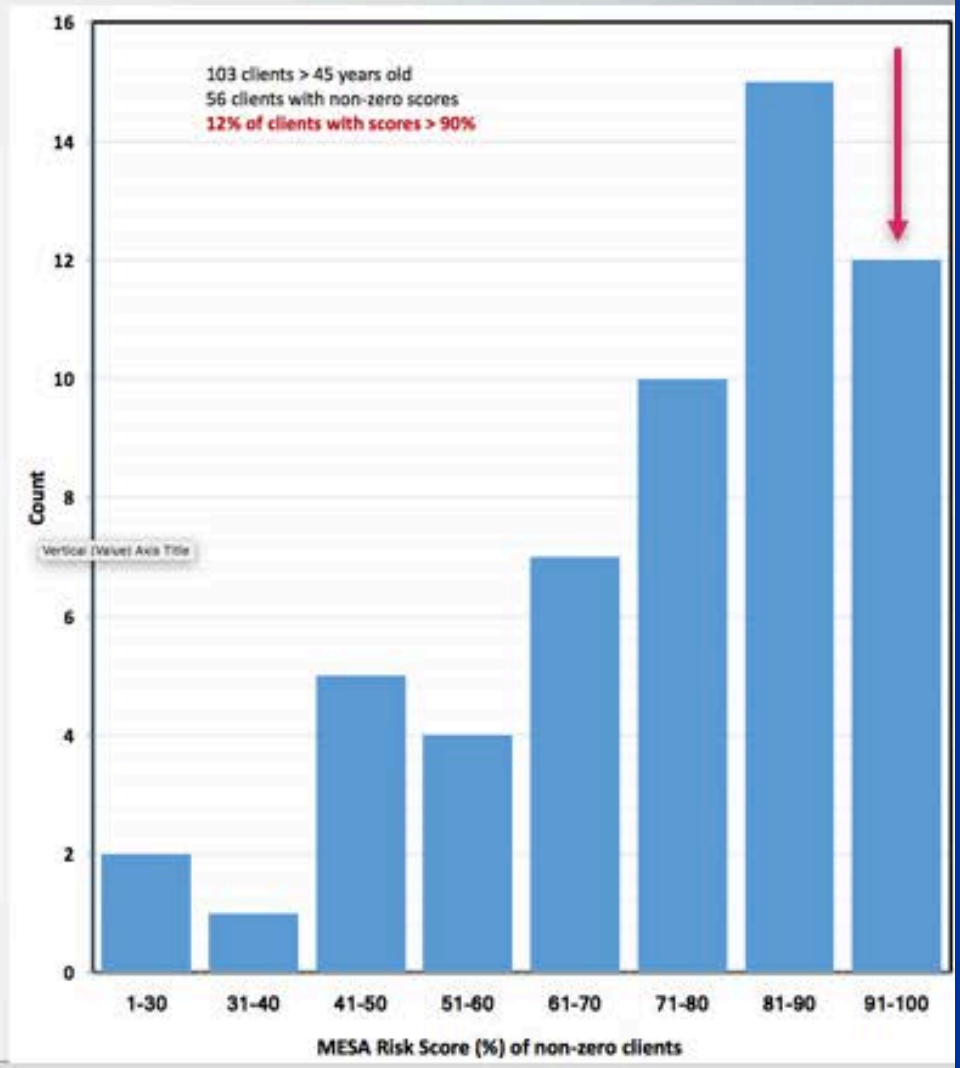
Left Ventricular Function		Absolute		Normalized*
Ejection Fraction	EF	62 %		
End Diastolic Volume	EDV	158 ml	EDVI	86 ml/m2
End Systolic Volume	ESV	60 ml	ESVI	33 ml/m2
Stroke Volume	SV	98 ml	SVI	53 ml/m2
Cardiac Output	CO	6.8 l/min	CI	3.7 l/min/m2
Average Heart Rate	HR	70 bpm		
Average Myocardial Mass	LVM	98.7 g	LVMI	53.8 g/m2
Std. Dev. Myocardial Mass	SD	3.9 g	SDI	2.1 g/m2
Myocardial Mass at ED	LVM ED	94.9 g	LVMI ED	51.7 g/m2
*Normalized to body surface area	BSA	1.83 m2		
Patient Height	H	1.69 m		
Patient Weight	W	73 kg		

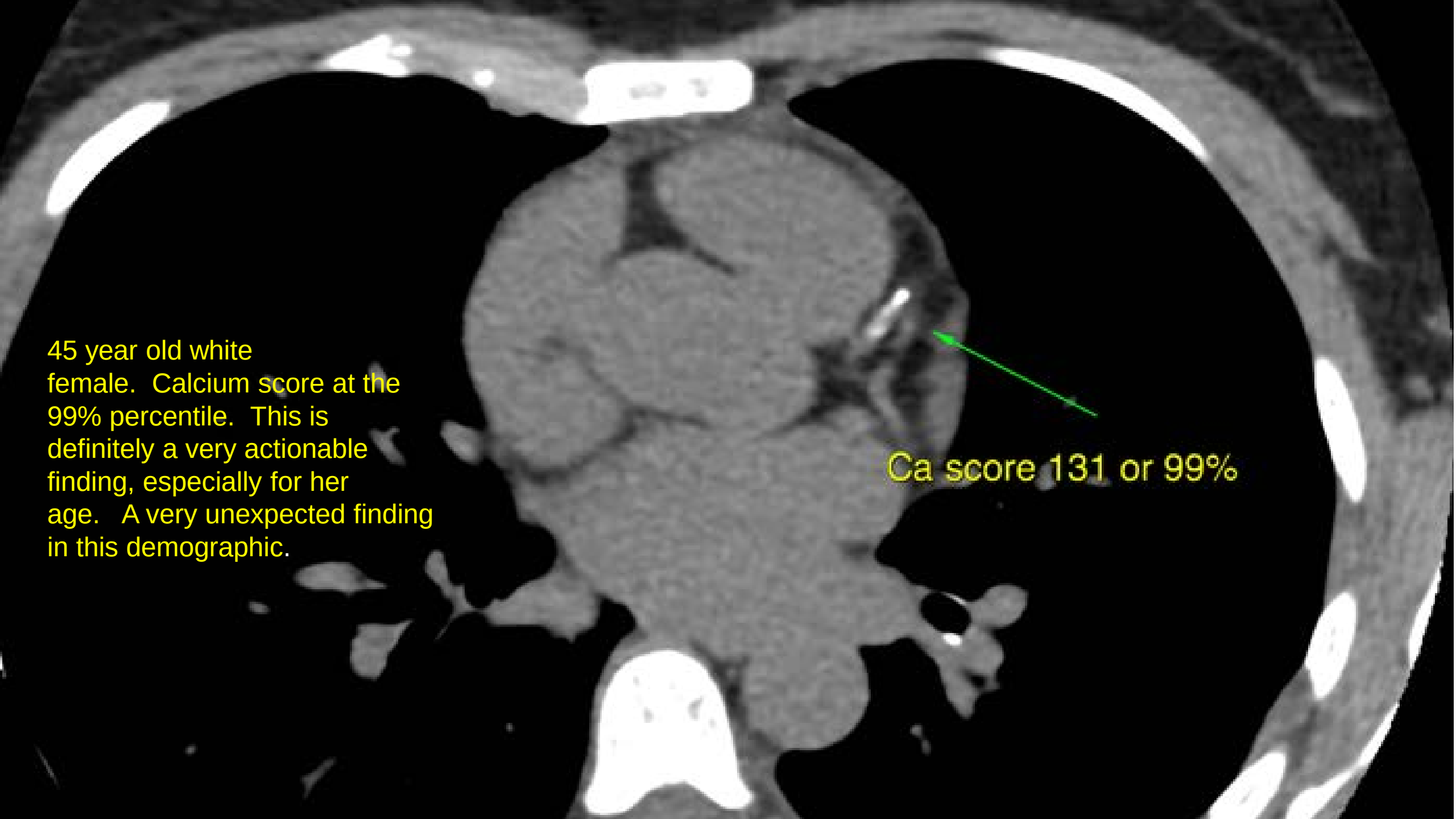
Functional output is automatically derived without technician or radiologist input

CT Scan for Coronary Artery Disease (CAD): Health Nucleus

- HN Clients screened = 103
- 12% of clients with scores > 90%
- More than half of those were less than age 60
- The 10-year CAD event risk is > 90% percentile for these clients
- We are detecting subclinical atherosclerosis in a significant fraction of our clients
- Some with scores that are quite elevated compared to their demographic

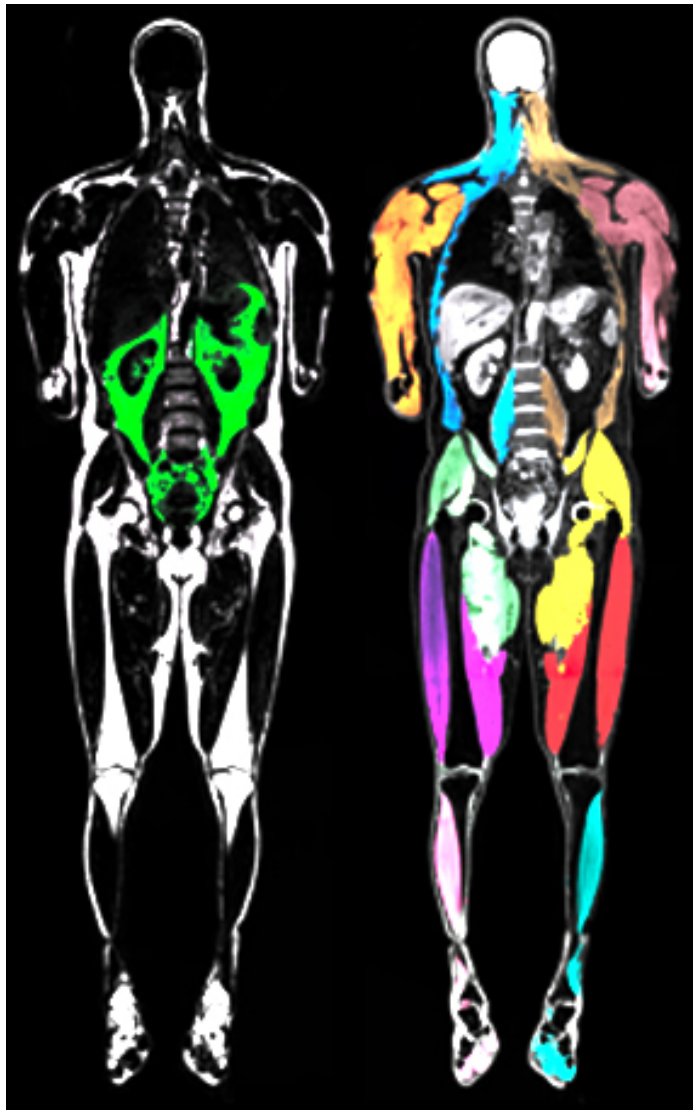






45 year old white female. Calcium score at the 99% percentile. This is definitely a very actionable finding, especially for her age. A very unexpected finding in this demographic.

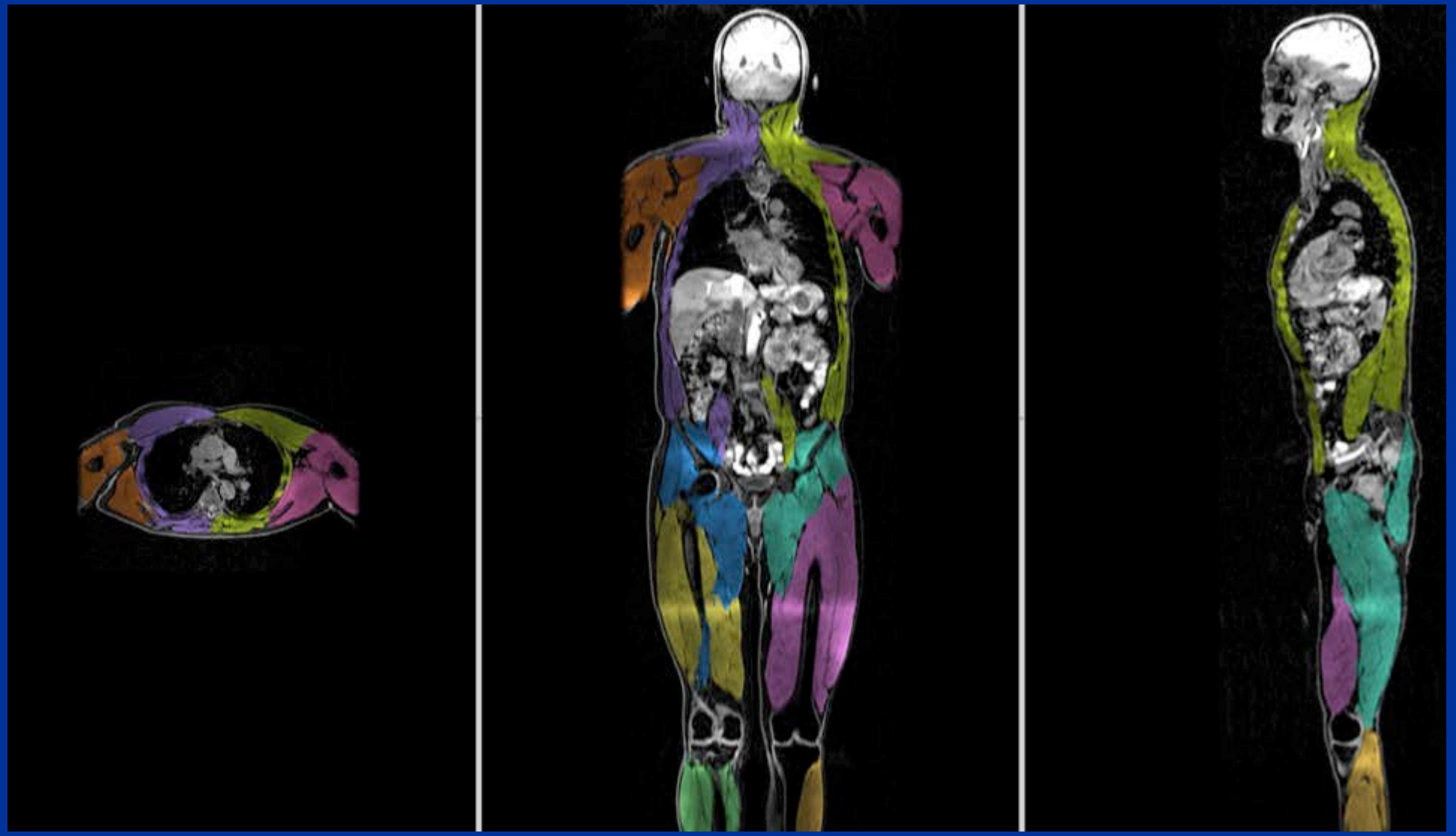
Combined Whole Body protocol: Fat and muscle quantification



Using the same WB protocol as on prior slide and via collaboration with **AMRA**:

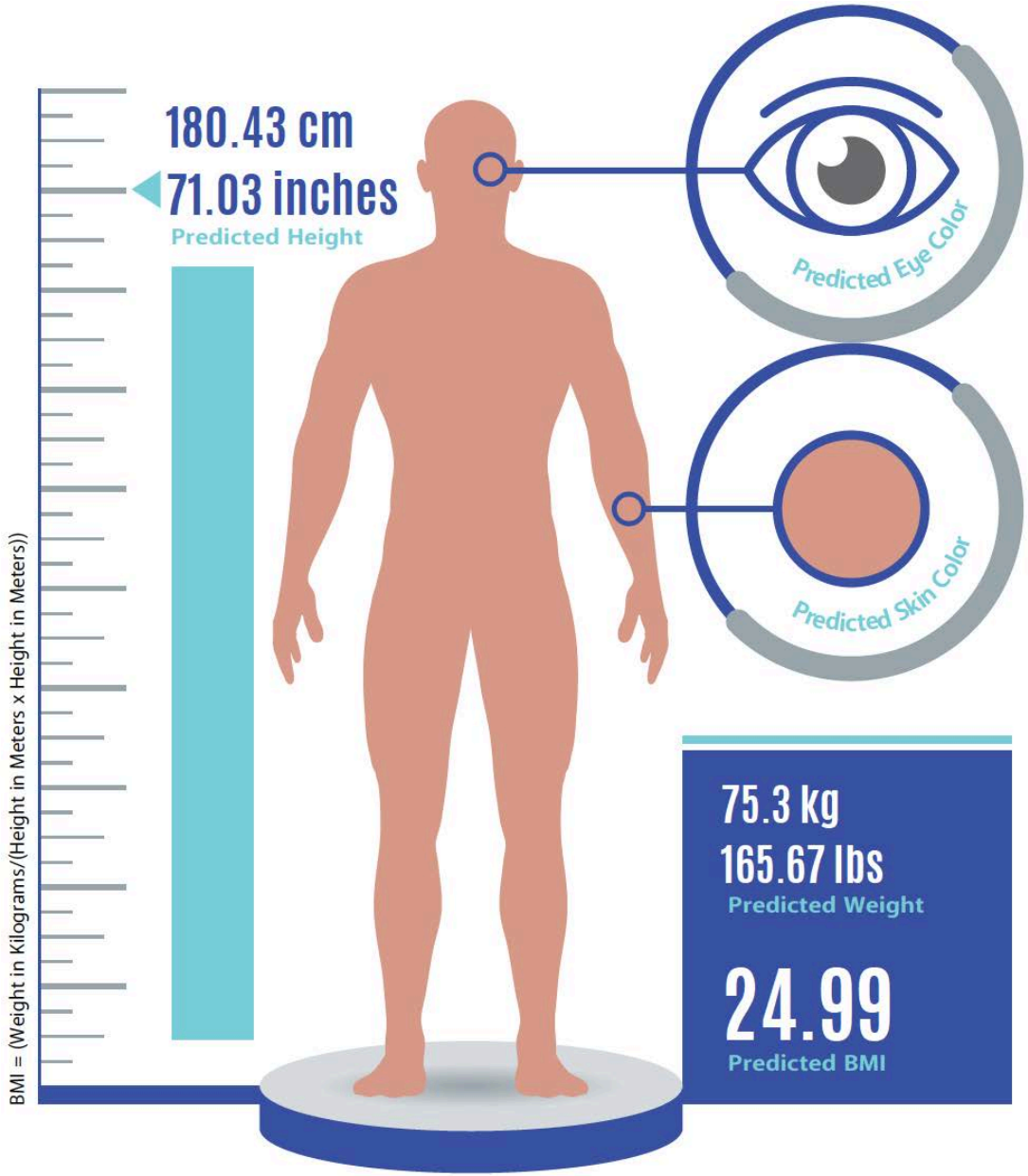
- Visceral Adipose Tissue (VAT, in liters)
- Abdominal Subcutaneous Adipose Tissue (ASAT, in liters)
- Total Adipose Tissue (TAT, in liters)
- Thigh Muscle Volume (in liters)
- Liver Fat (%)

Processed data: Segmented muscle volumes



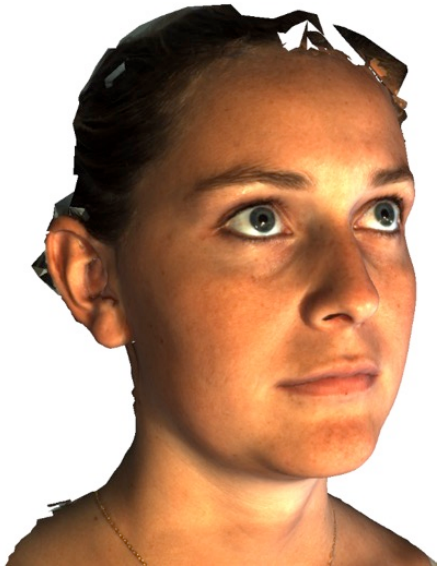
Machine Learning

Predicting everything that can be predicted from the genetic code



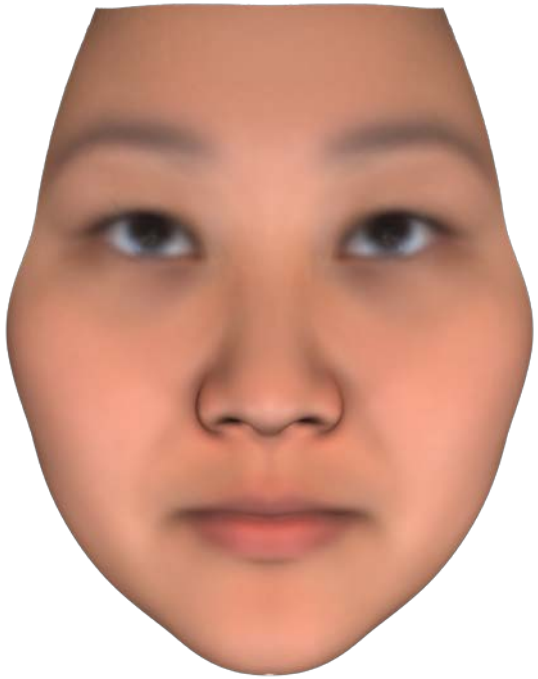
Actual	Height: N/A	Weight: N/A	BMI: 1

The Face Project

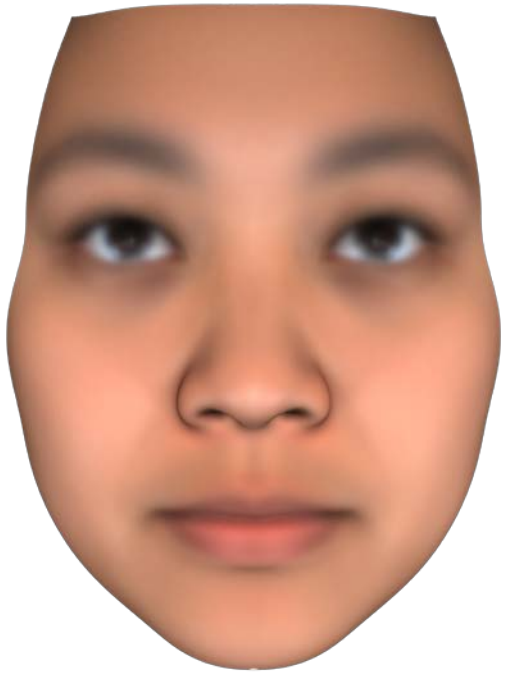


Genetic explanations for phenotype

- 3D images
- Voice
- Psychological information
- And others …



Subject



Prediction

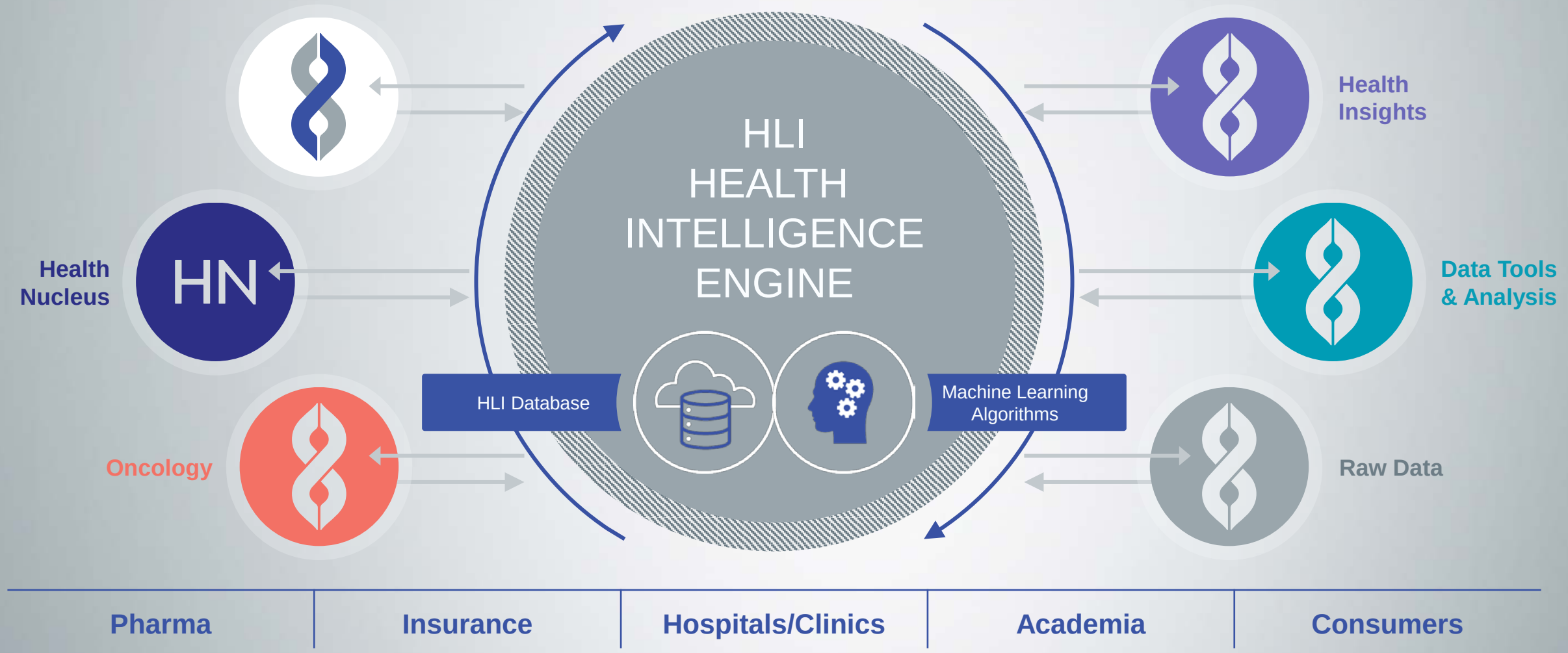
Subject

Prediction

Subject

Prediction

The HLI Health Intelligence Cycle



- Real time assessment of one or thousands of genomes
- Simple text in query line
- Provides state of the art annotation of variants with current knowledge (clinical, structural, genomic function)
- Plotting and genetic association analysis on the fly
- Curation tools to update knowledge
- Customization and ranking
- Supports machine learning analysis
- Has a CancerSearch dedicated version

Health Nucleus: PROACTIVE Curative AND Preventive Medicine

PROACTIVE Curative AND Preventive
Identify pathology and risk
Restore health and decrease risk
Promote individual (and family/community) service ethic
Clinical, behavioral, and social interventions

Medicine has been a clinical science, supported by data.

Medicine is about to become a data science, supported by clinicians.

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