IFHP 2022

From the alphabet of life to the grammar of health and disease

How genomic medicine is changing the payor's perspective'

Thomas D. Szucs

Helsana
Committed to life.

How can we achieve optimal health?

Modifiable drivers of health

Optimized (or not) based on behavior and structures/environments

Physical inputs
Diet
Supplementation
Substance use

Daily living
Productive activity
Social interaction
Content consumption
Hygiene

Movement
Ergonomics
Exercise
Sleep

Exposure
Nature
Atmosphere
Sensory
Materials
Stress

State of being
Mindsets/beliefs
Body composition
Material security

Healthcare
Vaccination
Detection/diagnosis
Treatment
Adherence

Less modifiable drivers of health

Genetics, traits, true randomness

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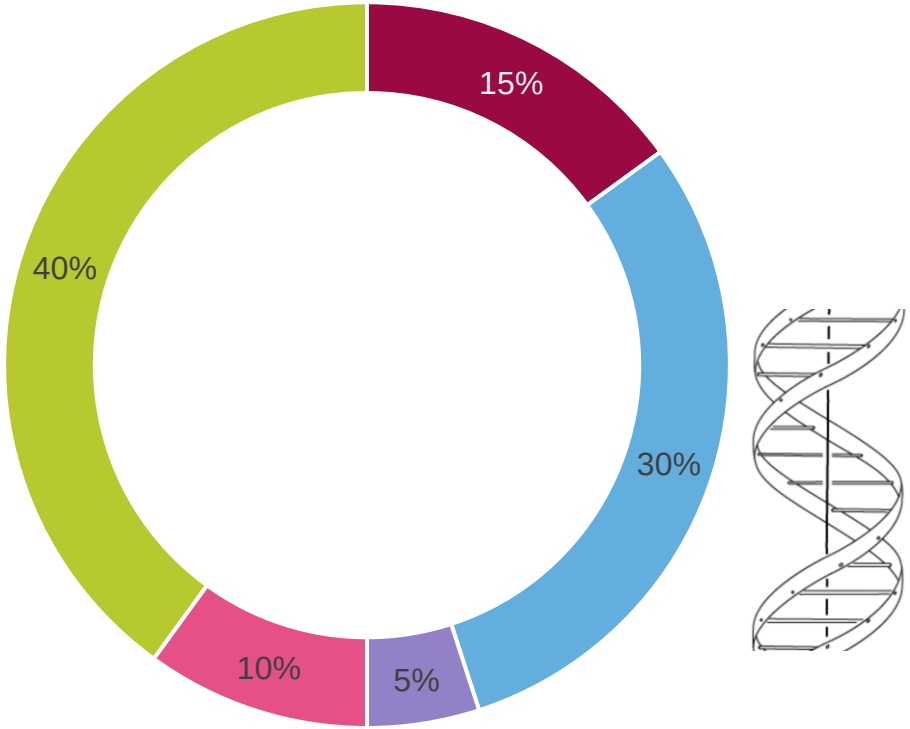
Determinants of premature death



Schroeder S 2007

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Will this impact the business?

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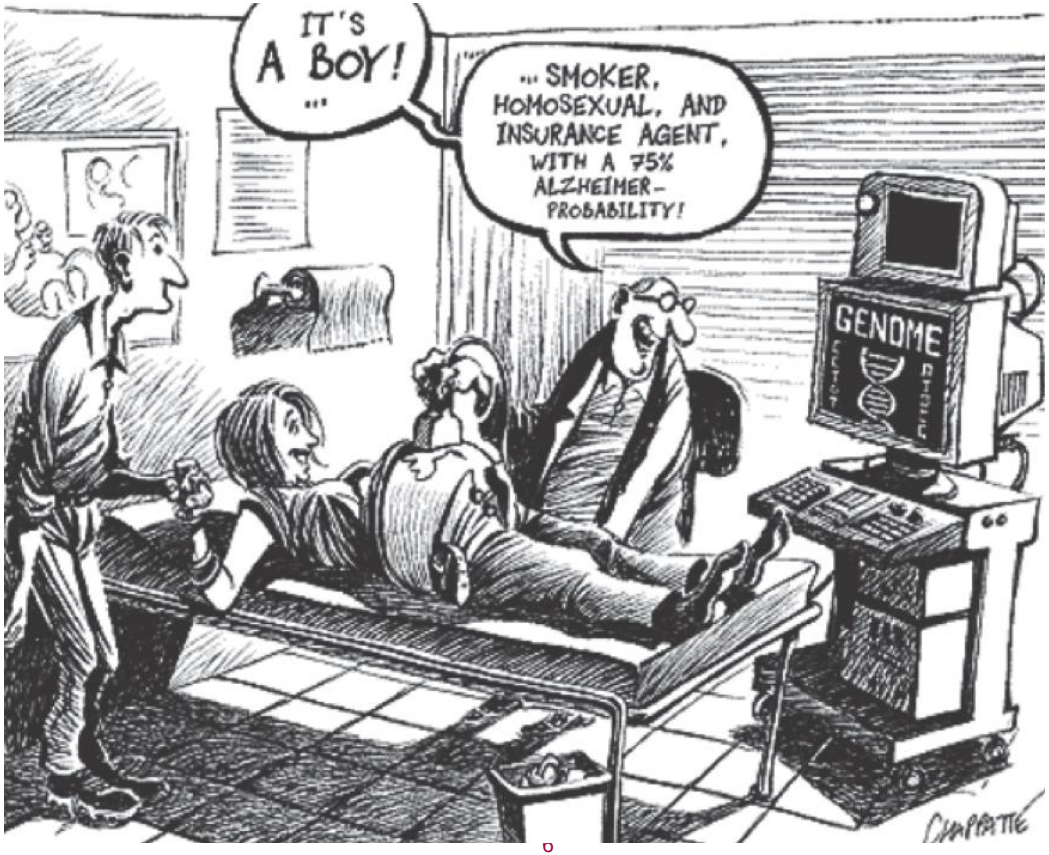
Will this impact my underwriter?



Will this impact my actuary?

PERSPECTIVE | AGING

The genetics of a long life

Genetically diverse mice and cross-species comparison uncover links to longevity

JOÃO PEDRO DE MAGALHÃES

SCIENCE • 29 Sep 2022 • Vol 377, Issue 6614 • pp. 1489-1490 • DOI: 10.1126/science.ade3119

Previously unknown loci associated with life span in mice may be relevant to humans living a long life, such as Emma Morano, who lived to 117 years. PHOTO: XINHUA NEWS AGENCY/CONTRIBUTOR/GETTY IMAGES

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HELIBERNINA

Overview

- Understanding the alphabet
- Understanding the grammar
- Using the manual in practice
- The payor's conundrum

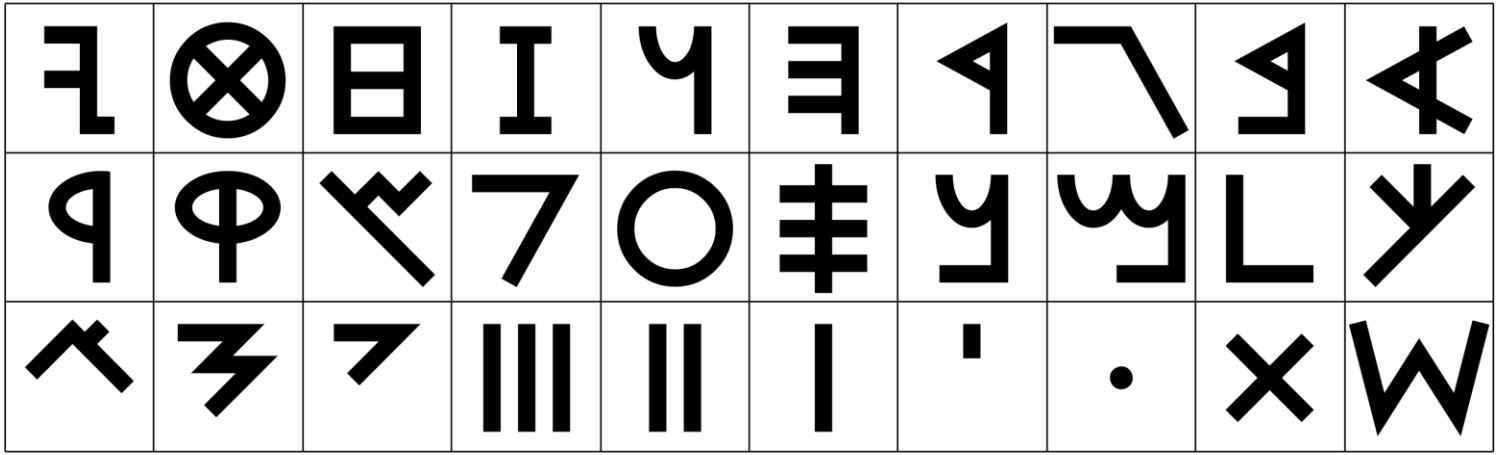
Overview

Understanding the alphabet

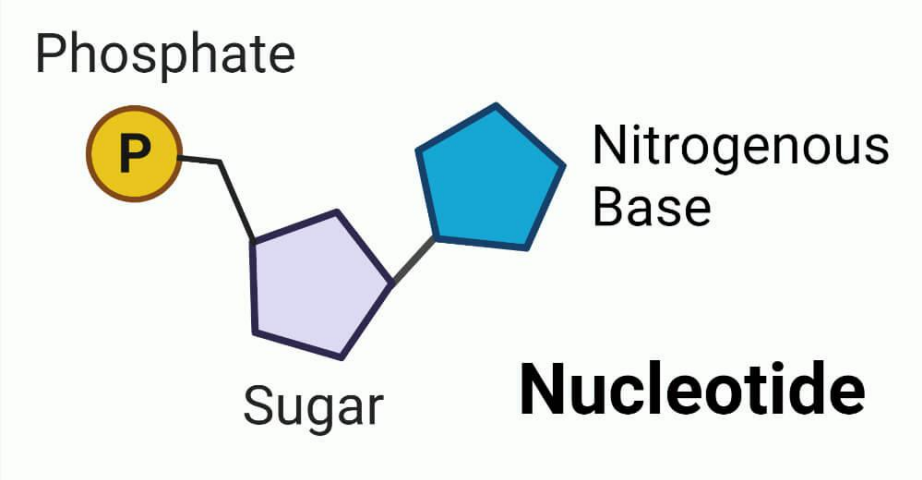
Understanding the grammar

Using the manual in practice

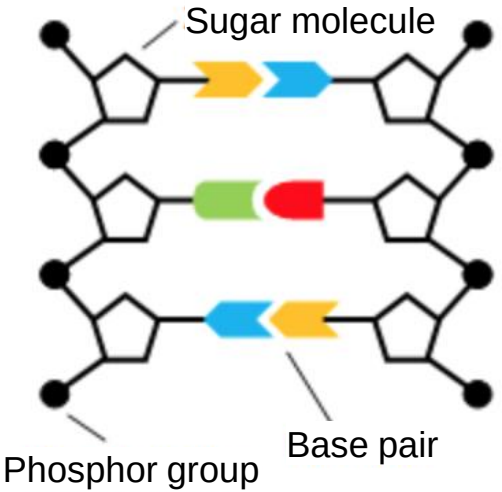
The payor's conundrum



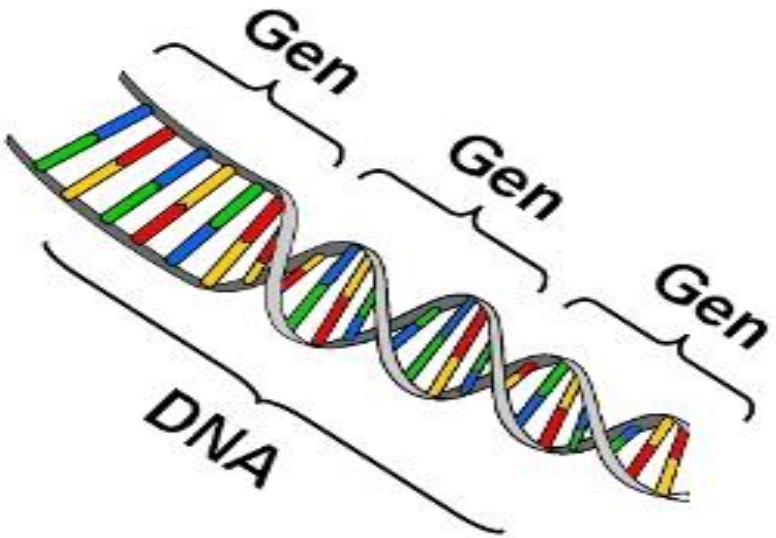
Letter = nucleotide



Word = Triplet, codon



Book = Gene



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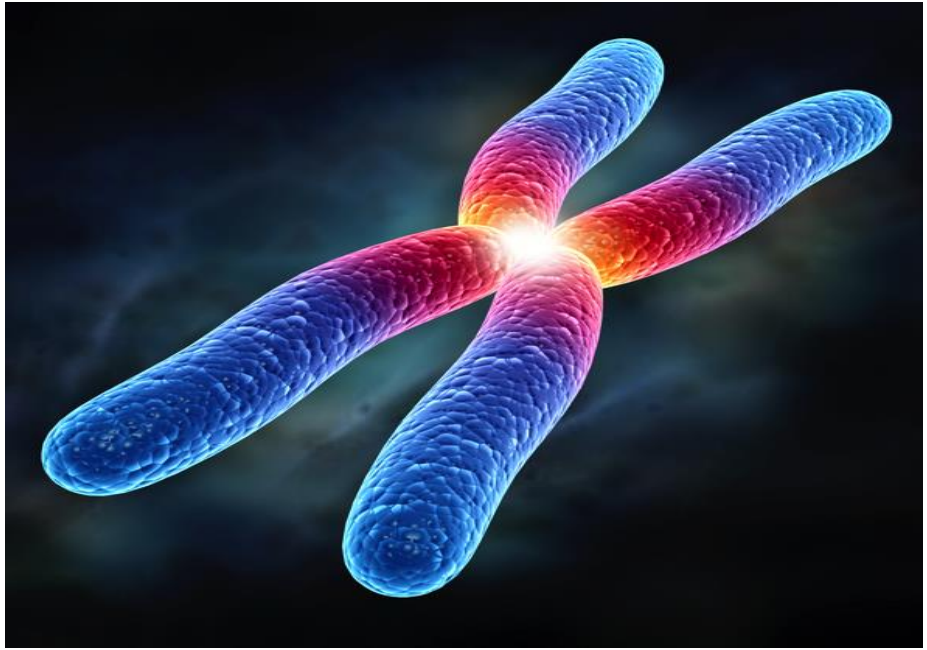
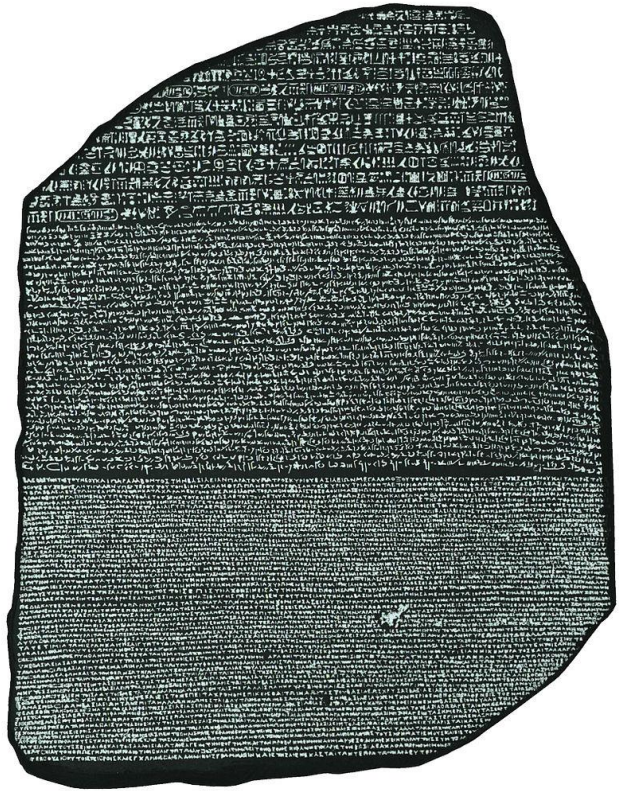
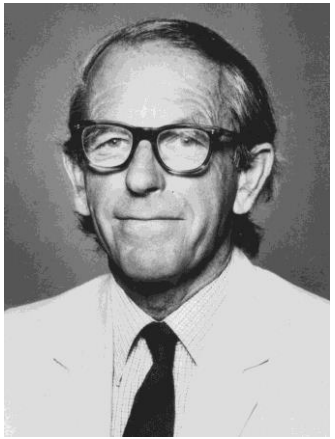
Book shelf = chromosome

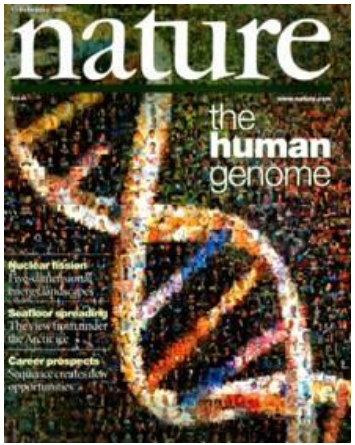


Library = Genome

Rosetta Stone of genomic medicine







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3.2 billion letters = ?

60 words/minute
8 hours / day

50 years

Overview

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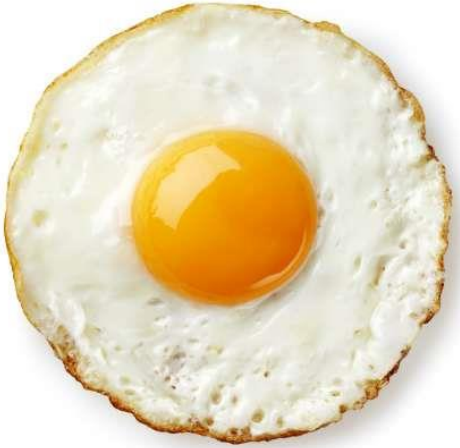
The payor's conundrum



Proteins, proteins, proteins . . .

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Exome = editorial content
Introns = advertising

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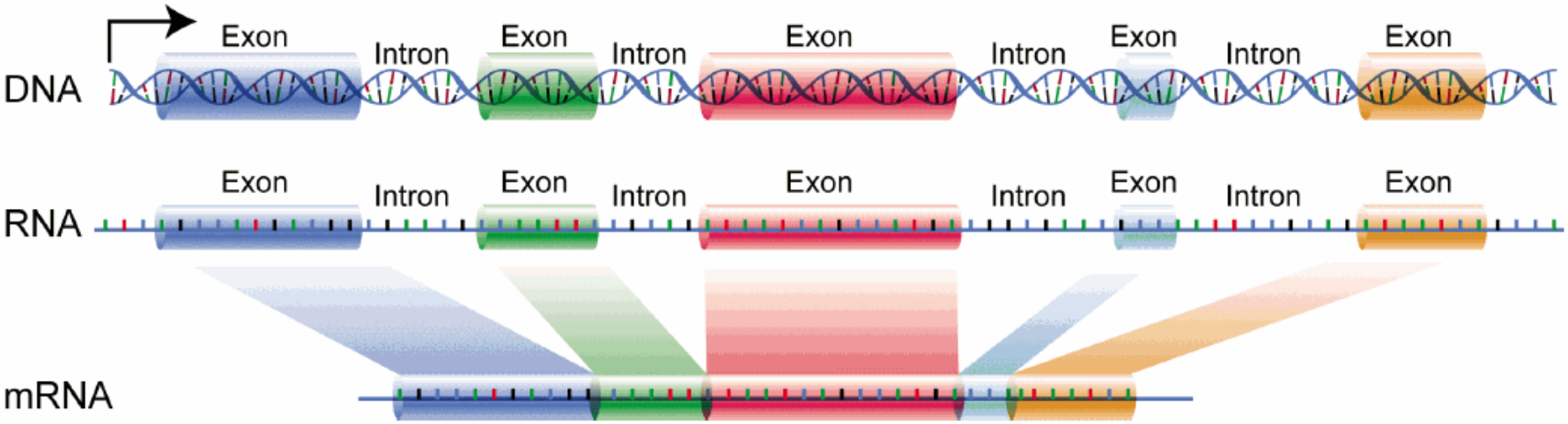
Exome = editorial content
Introns = advertising



Now we know:

Introns *are* really important

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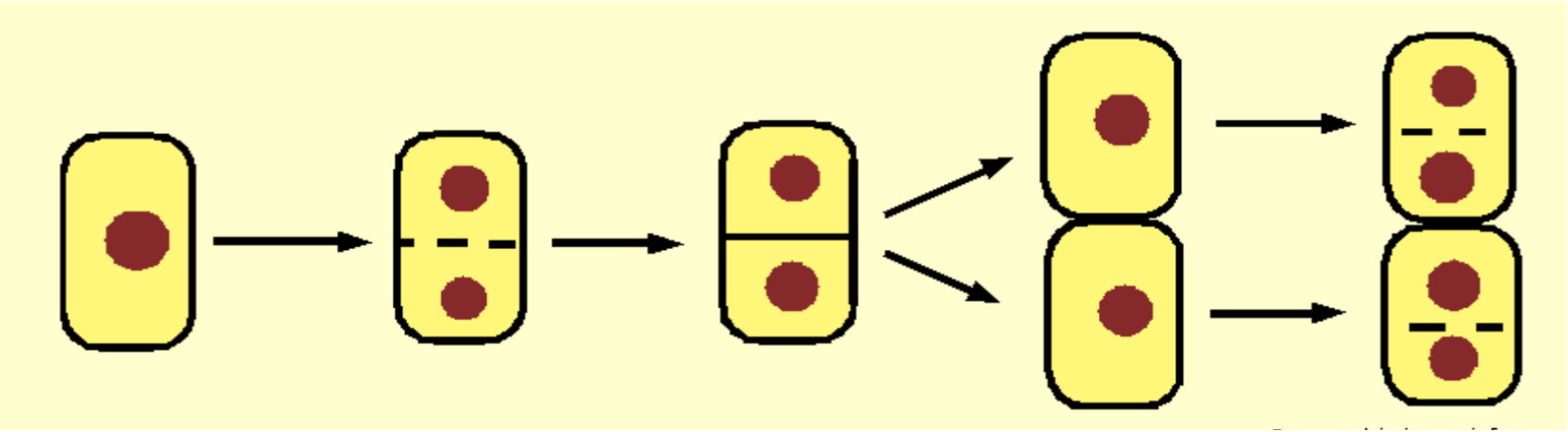
Mutations happen

≈ 175 mutations per diploid genome per generation.



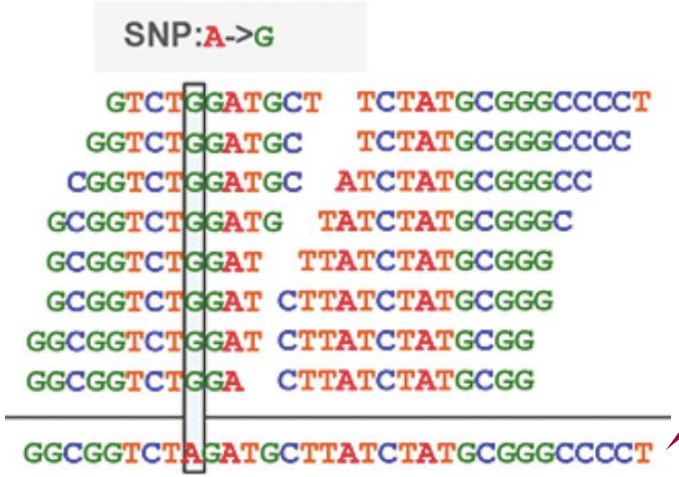
300 bn cell divisions / day

Composition of the genome

1.5% contains genes

10% regulates genes

Reference sequence is like a reference language *(lingua franca)*



Reference sequence

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New human reference genome T2T-CHM13 reveals greater diversity

Church DM 2022

IFHP 2022

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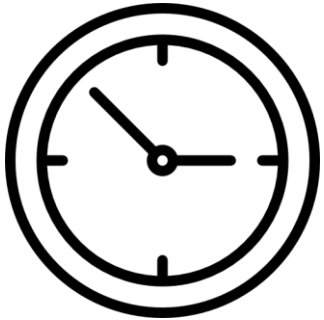
Next generation sequencing



Hours

< 5‘000 USD

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Next Generation Sequencing

Today

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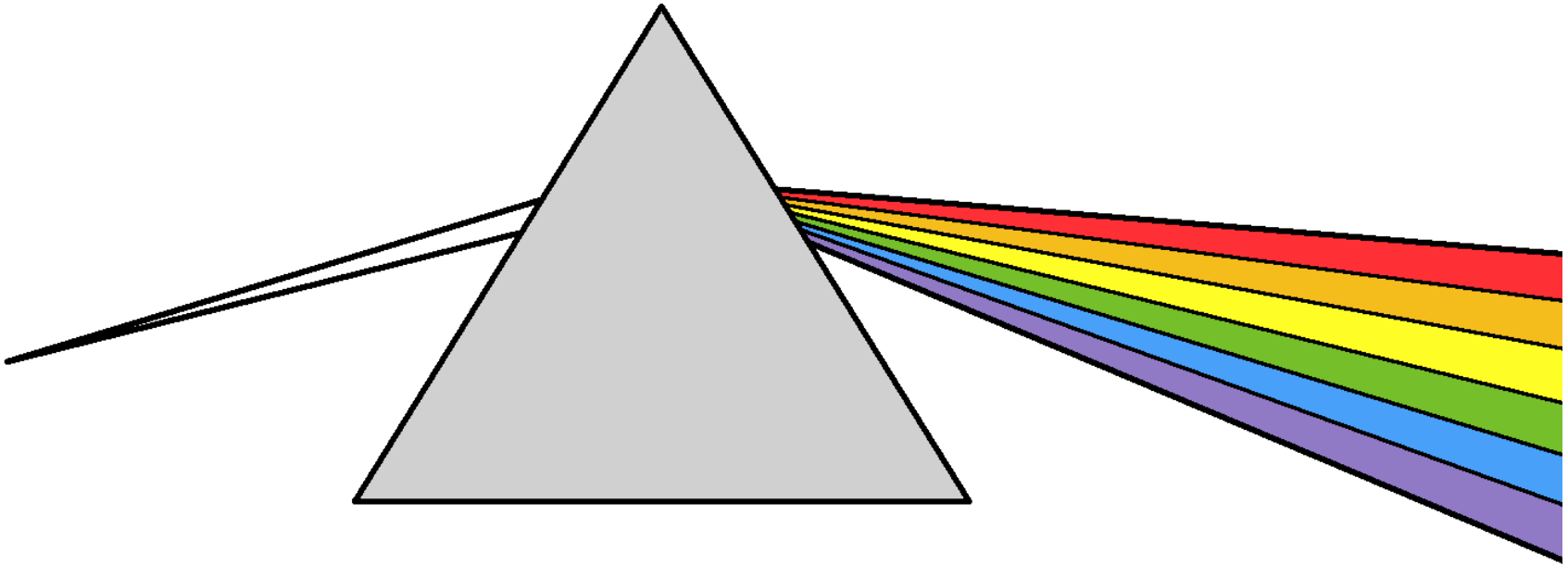
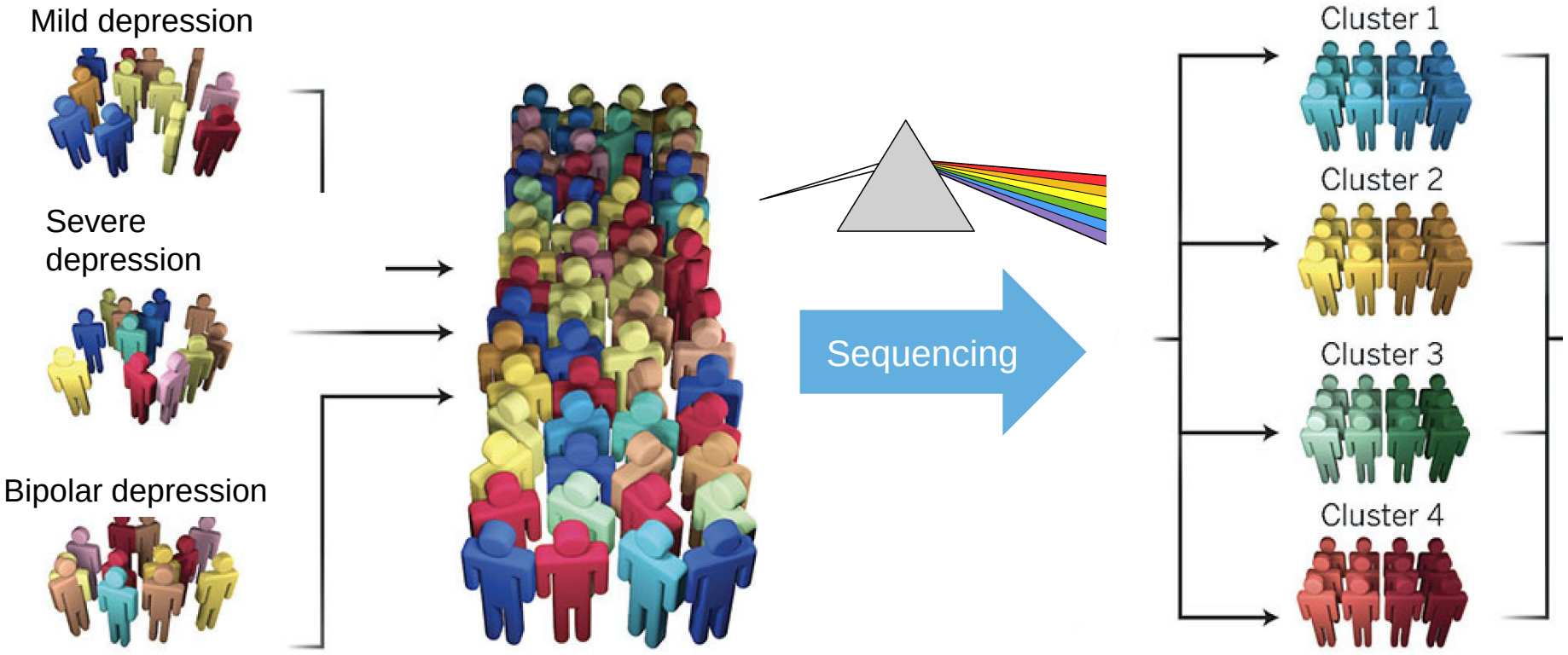
Sequencing is like using a prisma



Sequencing is like using a prisma



Insel TR 2015

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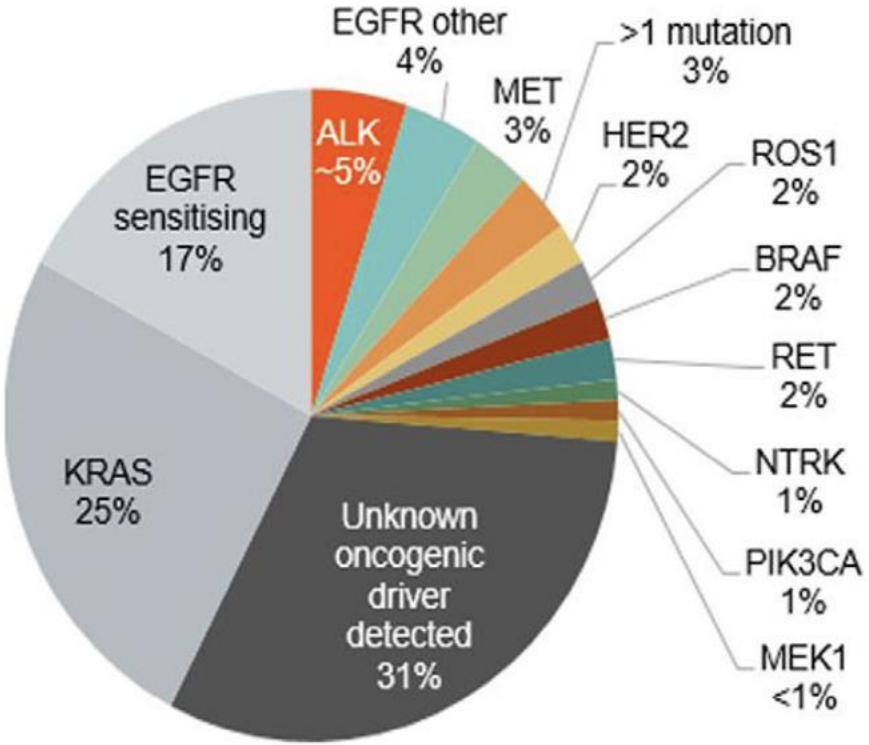
Mutations in lung cancer determine treatment options



Tsao AS 2016; Rosenquist R 2022

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Foundation one (Roche)

DNA GENE LIST: ENTIRE CODING SEQUENCE FOR THE DETECTION OF BASE SUBSTITUTIONS, INSERTION/DELETIONS, AND COPY NUMBER ALTERATIONS

ABL1	*ACVR1B*	*AKT1*	*AKT2*	*AKT3*	*ALK*	*ALOX12B*	*ATRX*	*AMER1 (FAM123B)*
APC	*AR*	*ARAF*	*ARFRP1*	*ARID1A*	*ASXL1*	*ATM*	*ATR*	*AURKA*
AURKB	*AXIN1*	*AXL*	*BAP1*	*BARD1*	*BCL2*	*BCL2L1*	*BCL2L2*	*BCL6*
BCOR	*BCORL1*	*BRAF*	*BRCA1*	*BRCA2*	*BRD4*	*BRIP1*	*BTG1*	*BTG2*
BTK	*C1orf30 (EMSY)*	*C17orf39 (GID4)*	*CALR*	*CARD11*	*CASP8*	*CBFB*	*CBL*	*CCND1*
CCND2	*CCND3*	*CCNE1*	*CD22*	*CD274 (PD-L1)*	*CD70*	*CD79A*	*CD79B*	*CDC73*
CDH1	*CDK12*	*CDK4*	*CDK6*	*CDK8*	*CDKN1A*	*CDKN1B*	*CDKN2A*	*CDKN2B*
CDKN2C	*CEBPA*	*CHEK1*	*CHEK2*	*CIC*	*CREBBP*	*CRKL*	*CSF1R*	*CSF3R*
CTCF	*CTNNA1*	*CTNNB1*	*CUL3*	*CUL4A*	*CXCR4*	*CYP17A1*	*DAXX*	*DDR1*
DDR2	*DIS3*	*DNMT3A*	*DOT1L*	*EED*	*EGFR*	*EP300*	*EPHA3*	*EPHB1*
EPHB4	*ERBB2*	*ERBB3*	*ERBB4*	*ERCC4*	*ERG*	*ERRFI1*	*ESR1*	*EZH2*
FAM46C	*FANCA*	*FANCC*	*FANCG*	*FANCL*	*FAS*	*FBXW7*	*FGF10*	*FGF12*
FGF14	*FGF19*	*FGF23*	*FGF3*	*FGF4*	*FGF6*	*FGFR1*	*FGFR2*	*FGFR3*
FGFR4	*FH*	*FLCN*	*FLT1*	*FLT3*	*FOXL2*	*FUBP1*	*GABRA6*	*GATA3*
GATA4	*GATA6*	*GNA11*	*GNA13*	*GNAQ*	*GNAS*	*GRM3*	*GSK3B*	*H3F3A*
HDAC1	*HGF*	*HNF1A*	*HRAS*	*HSD3B1*	*ID3*	*IDH1*	*IDH2*	*IGF1R*
IKBKE	*IKZF1*	*INPP4B*	*IRF2*	*IRF4*	*IRS2*	*JAK1*	*JAK2*	*JAK3*
JUN	*KDM5A*	*KDM5C*	*KDM6A*	*KDR*	*KEAP1*	*KEL*	*KIT*	*KLHL6*
KMT2A (MLL)	*KMT2D (MLL2)*	*KRAS*	*LTK*	*LYN*	*MAF*	*MAP2K1 (MEK1)*	*MAP2K2 (MEK2)*	*MAP2K4*
MAP3K1	*MAP3K13*	*MAPK1*	*MCL1*	*MDM2*	*MDM4*	*MED12*	*MEF2B*	*MEN1*
MERTK	*MET*	*MITF*	*MKNK1*	*MLH1*	*MPL*	*MRE11A*	*MSH2*	*MSH3*
MSH6	*MST1R*	*MTAP*	*MTOR*	*MUTYH*	*MYC*	*MYCL (MYCL1)*	*MYCN*	*MYD88*
NBN	*NF1*	*NF2*	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOTCH1*	*NOTCH2*	*NOTCH3*
NPM1	*NRAS*	*NTSC2*	*NTRK1*	*NTRK2*	*NTRK3*	*P2RY8*	*PALB2*	*PARK2*
PARP1	*PARP2*	*PARP3*	*PAXS*	*PBRM1*	*PDCD1 (PD1)*	*PDCD1LG2 (PD-L2)*	*PDGFRA*	*PDGFRB*
PDK1	*PIK3C2B*	*PIK3C2G*	*PIK3CA*	*PIK3CB*	*PIK3R1*	*PIM1*	*PMS2*	*POLD1*
POLE	*PPARG*	*PPP2R1A*	*PPP2R2A*	*PRDM1*	*PRKAR1A*	*PRKCI*	*PTCH1*	*PTEN*
PTPN11	*PTPRO*	*QKI*	*RAC1*	*RAD21*	*RAD51*	*RAD51B*	*RAD51C*	*RAD51D*
RAD52	*RAD54L*	*RAF1*	*RARA*	*RB1*	*RBM10*	*REL*	*RET*	*RICTOR*
RNF43	*ROS1*	*RPTOR*	*SDHA*	*SDHB*	*SDHC*	*SDHD*	*SETD2*	*SF3B1*
SGK1	*SMAD2*	*SMAD4*	*SMARCA4*	*SMARCB1*	*SMO*	*SNCAIP*	*SOCS1*	*SOX2*
SOX9	*SPEN*	*SPOP*	*SRC*	*STAG2*	*STAT3*	*STK11*	*SUFU*	*SYK*
TBX3	*TEK*	*TET2*	*TGFBR2*	*TIPARP*	*TNFAIP3*	*TNFRSF14*	*TP53*	*TSC1*
TSC2	*TYRO3*	*U2AF1*	*VEGFA*	*VHL*	*WHSC1*	*WHSC1L1*	*WT1*	*XPO1*
XRCC2	*ZNF217*	*ZNF703*						

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

ALK	*BCL2*	*BCR*	*BRAF*	*BRCA1*	*BRCA2*	*CD74*	*KIT*	*EGFR*
ETV4	*ETV5*	*ETV6*	*EWSR1*	*EZR*	*FGFR1*	*FGFR2*	*FGFR3*	*KMT2A (MLL)*
MSH2	*MYB*	*MYC*	*NOTCH2*	*NTRK1*	*NTRK2*	*NUTM1*	*PDGFRA*	*RAF1*
RARA	*RET*	*ROS1*	*RSPO2*	*SDC4*	*SLC34A2*	*TERC**	*TERT***	*TMPRSS2*

*TERC is an ncRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER GENOMIC SIGNATURES

Microsatellite (MS) status

Tumor Mutational Burden (TMB)

FOUNDATIONONE®CDx

PATIENT Sample, Jane

TUMOR TYPE Lung adenocarcinoma

REPORT DATE 01 Jan 2018

PRF# XXXXXXXX

ABOUT THE TEST FoundationOne®CDx is a next-generation sequencing (NGS) based assay that identifies genomic findings within hundreds of cancer-related genes.

PATIENT

DISEASE Lung adenocarcinoma
NAME Not Given
DATE OF BIRTH Not Given
SEX Not Given
MEDICAL RECORD # Not Given

PHYSICIAN

ORDERING PHYSICIAN Not Given
MEDICAL FACILITY Not Given
ADDITIONAL RECIPIENT Not Given
MEDICAL FACILITY ID Not Given
PATHOLOGIST Not Given

SPECIMEN

SPECIMEN SITE Not Given
SPECIMEN ID Not Given
SPECIMEN TYPE Not Given
DATE OF COLLECTION Not Given
SPECIMEN RECEIVED Not Given

Genomic Signatures

Microsatellite status - MS-Stable
Tumor Mutational Burden - TMB-Low (4 Muts/Mb)

Gene Alterations

For a complete list of the genes assayed, please refer to the Appendix.

ALK EML4-ALK fusion (Variant 1)
CCND1 amplification
FGF19 amplification
FGF3 amplification
FGF4 amplification
NFKBIA amplification
NKX2-1 amplification
TP53 R306*

7 Disease-relevant genes with no reportable alterations: ***EGFR, KRAS, BRAF, MET, RET, ERBB2, ROS1***

6 Therapies Approved in the EU
0 Therapies with Lack of Response
14 Clinical Trials

GENOMIC SIGNATURES	ACTIONABILITY
Microsatellite status - MS-Stable	No therapies or clinical trials. see Genomic Signatures section
Tumor Mutational Burden - TMB-Low (4 Muts/Mb)	No therapies or clinical trials. see Genomic Signatures section

GENE ALTERATIONS	THERAPIES APPROVED IN THE EU (IN PATIENT'S TUMOR TYPE)	THERAPIES APPROVED IN THE EU (IN OTHER TUMOR TYPE)
ALK - EML4-ALK fusion (Variant 1)	Alectinib	None
	Ceritinib	
10 Trials see p. 11	Crizotinib	
CCND1 - amplification	None	Abemaciclib
		Palbociclib
4 Trials see p. 14		Ribociclib

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Geisinger Health System

GEISINGER

Williams MS 2019

MyCode® Community Health Initiative

227,000 consented participants

Sequencing completed on 92,000

Approximately 2% actionable genotypes

Being a carrier for a genetic condition is very common

23‘543 individuals

Testing on 108 recessive disorders

24% carriers for at least *one* disorder

5.5% carriers for *multiple* disorders

Lazarin GA 2013

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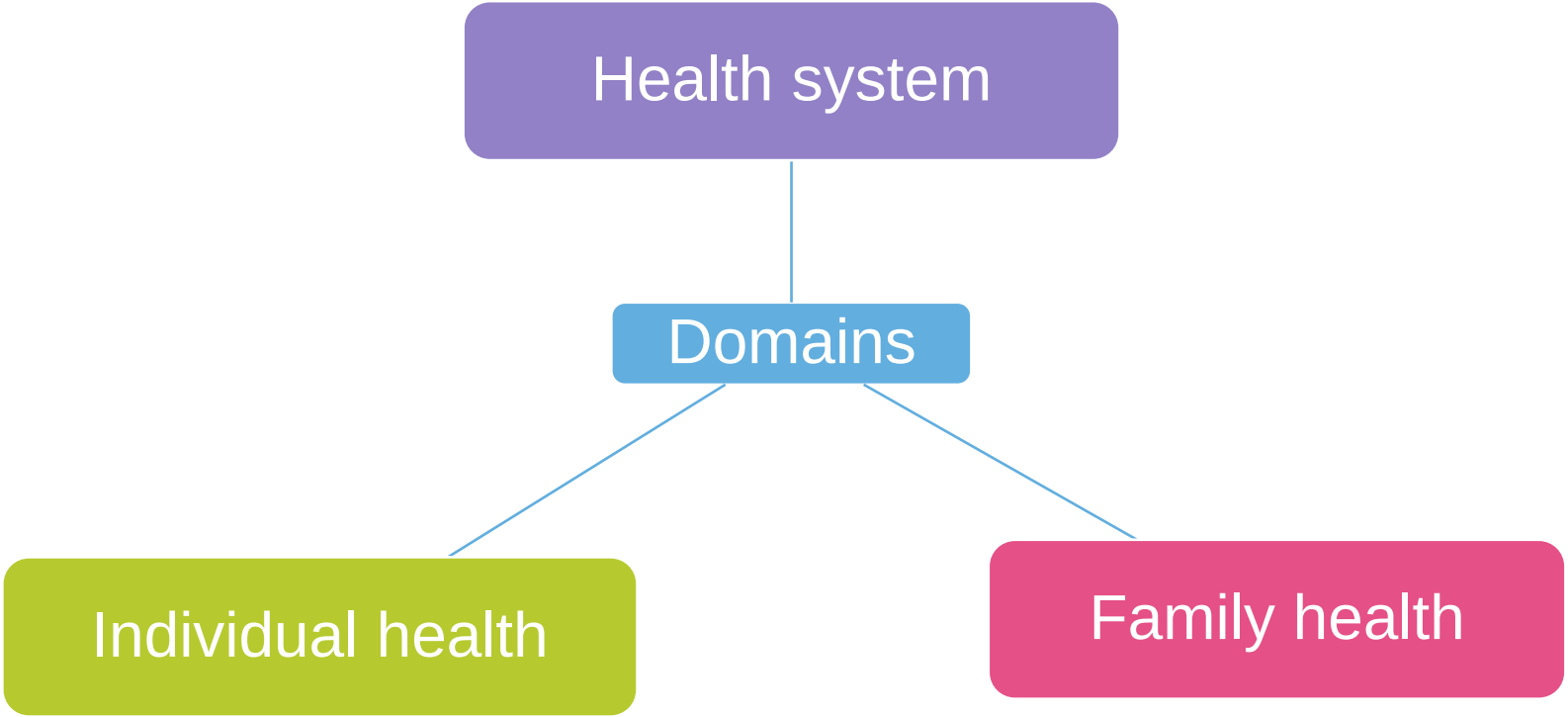
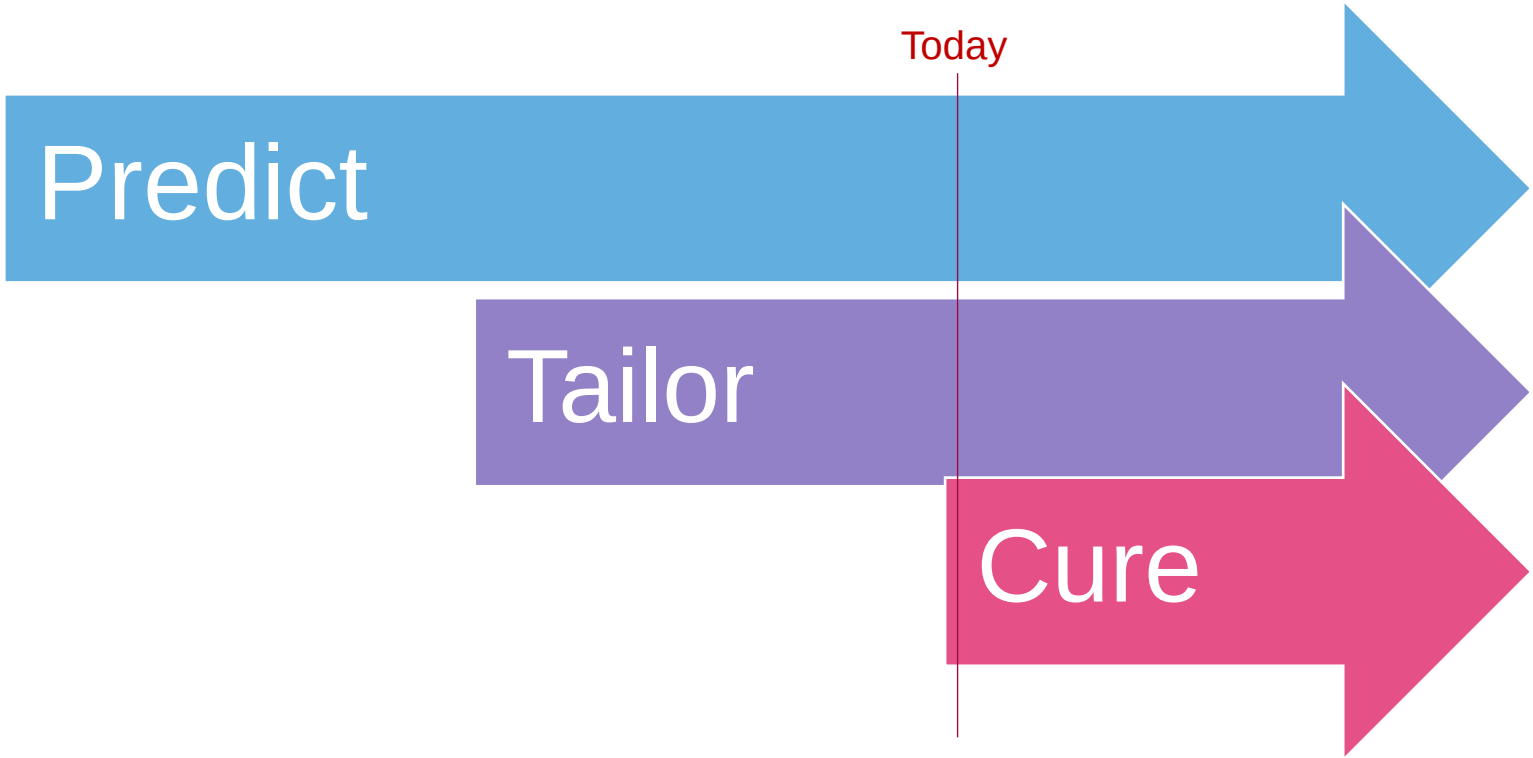
Genomic medicines touches all domains of healthcare system



Where is genomic medicine heading?



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Genomic medicine is learning from large datasets

17 hospitals, >100‘000 patients, >3000 physicians and 1 hightech sequencing lab

HIRSLANDEN PRECISE

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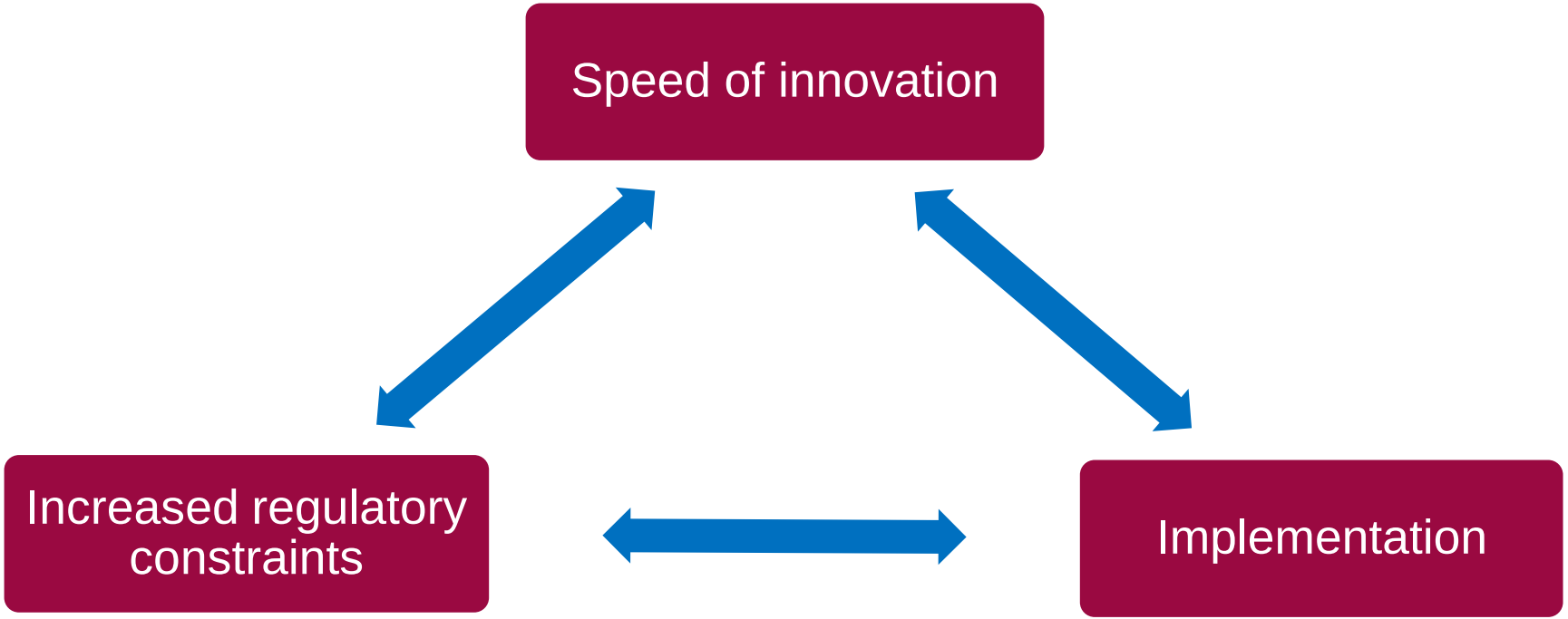
Future of genomic medicine for payors will depend on three important factors



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Enabling digital technologies across the clinical genomics pathway

Bombard Y 2022

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Digital technologies across the clinical genomics pathway

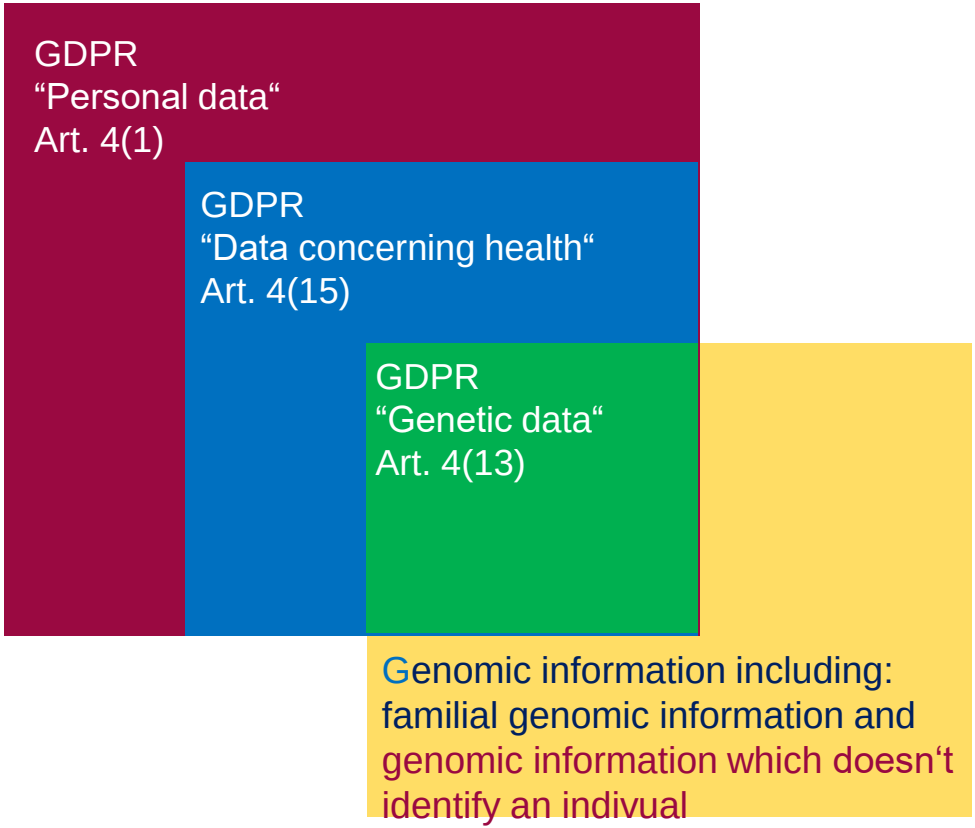
Bombard Y 2022

Greatest regulatory impact on genomic medicine

Data privacy and cyber security

Artificial intelligence

GDPR and genomic information



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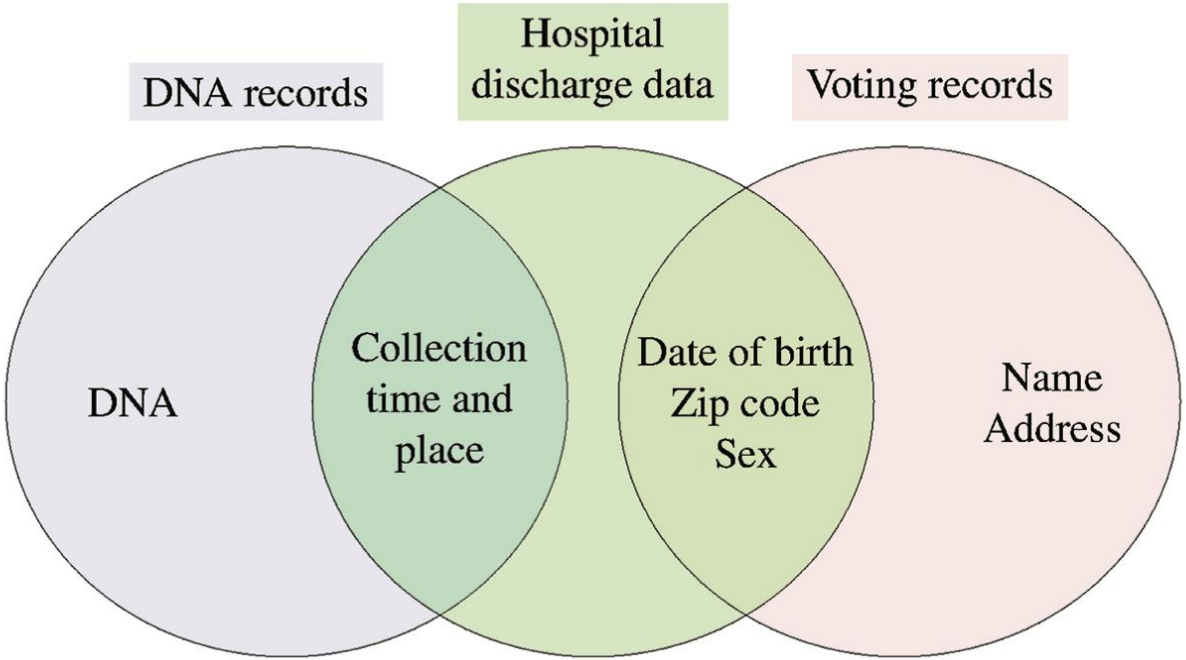
„Genomic information which doesn‘t identify an indivual.“

Is this possible?

De-anonymisation has become easy



Malin & Sweeney 2004

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From genotype to phenotype

Real (*Left*) and predicted (*Right*) faces

Lippert C 2017

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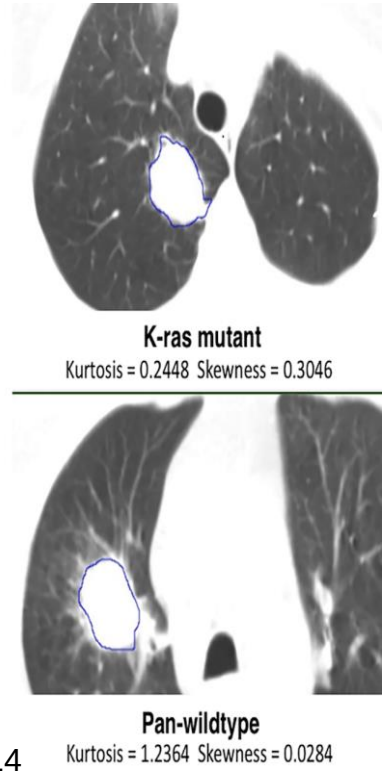
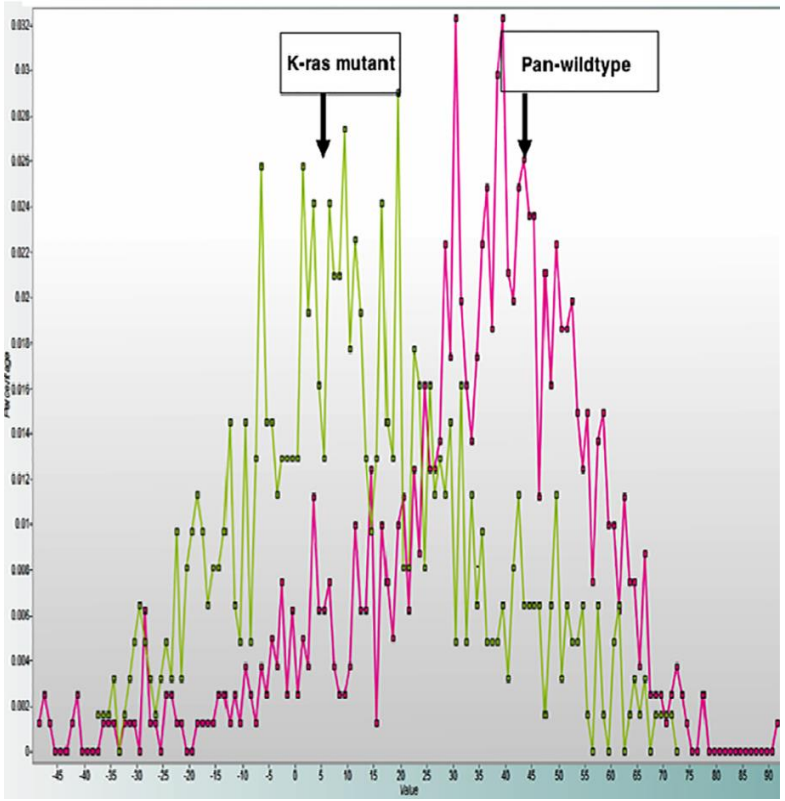
From phenotype to genotype





Weiss GJ 2014

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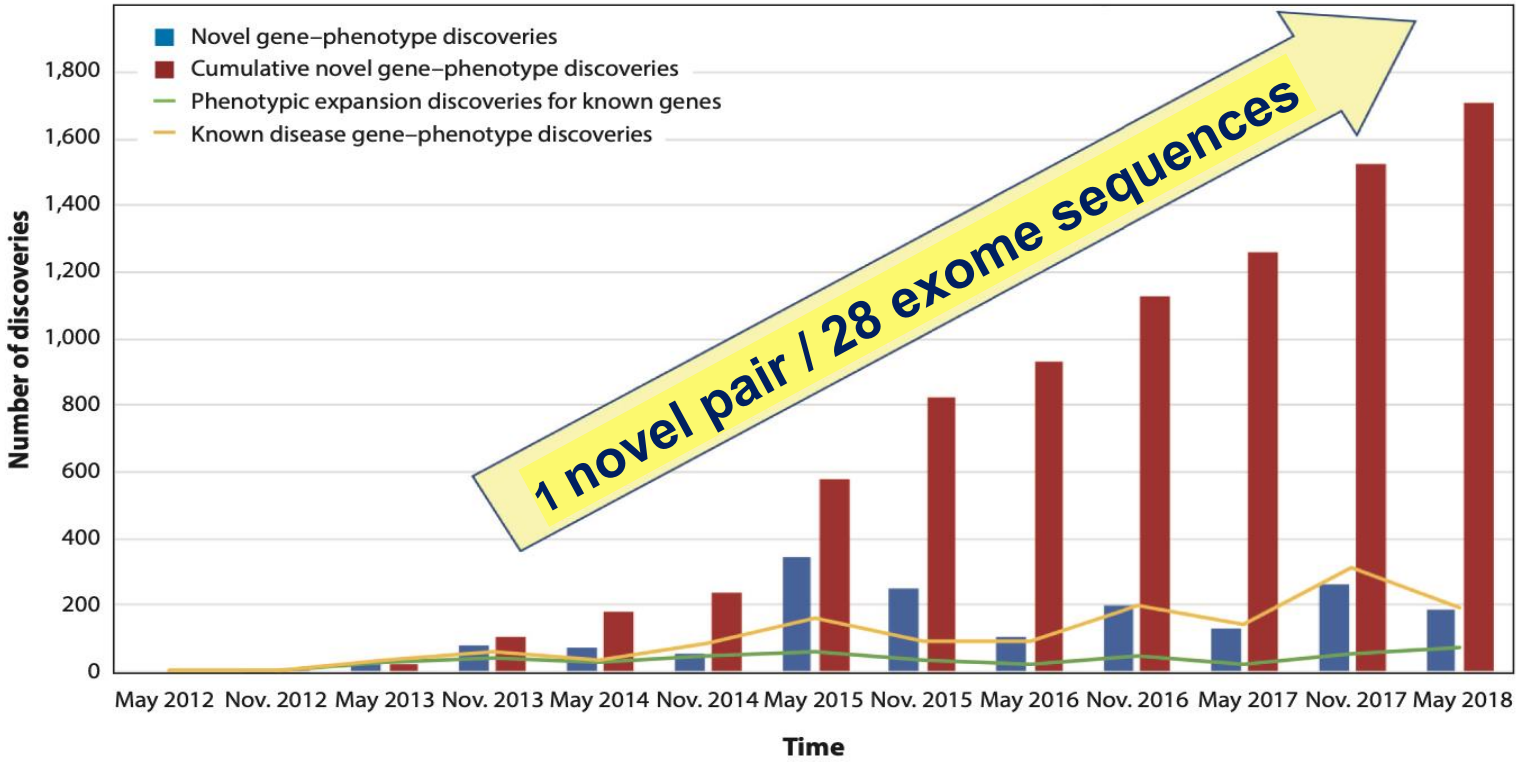
Discovery of 263 novel gene–phenotype pairs annually



Amendola LM 2021

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Data sanitization

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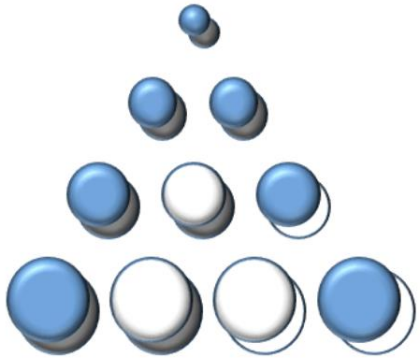
https://gddp.research.cchmc.or



GDDP

Genetic Disease Diagnosis based on Phenotypes

Welcome to GDDP, computational Genetic Disease Diagnosis based on Phenotypes.

Face2Gene App: 4000 genetic diseases

FACE2GENE

60% of human geneticists use this app already

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AI Regulations on the verge

EU White Paper

Council of Europe

EU Act

OECD Recommendations

KEEP
CALM
AND
THINK
AHEAD

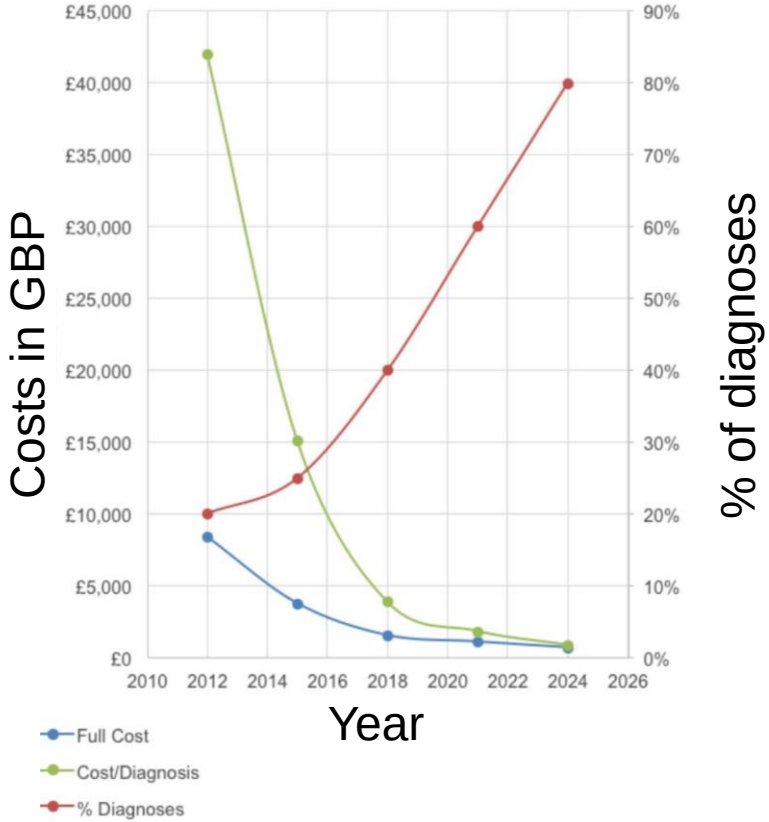
Payors do not want to pay for …

… long and inefficient diagnostic journeys.

… expensive drugs that do not work.

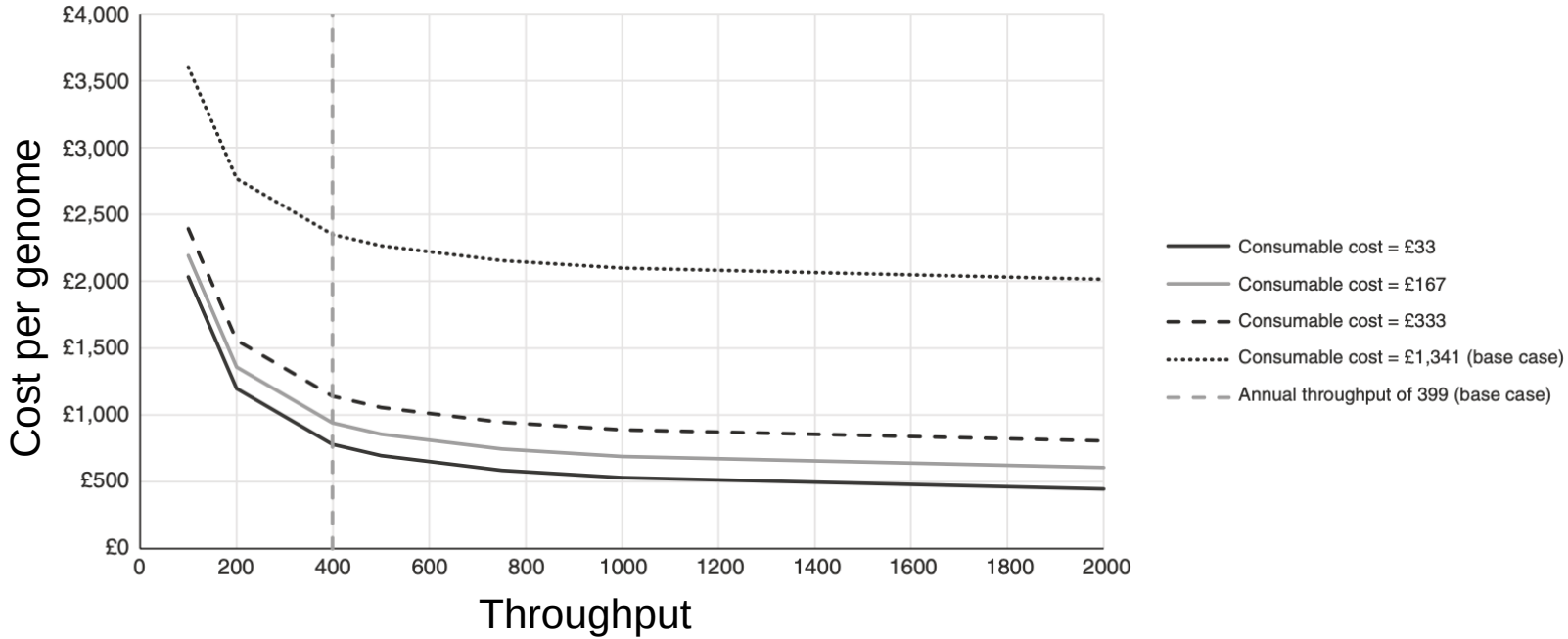
… unsafe health care.

Reducing diagnostic odyssies



Helsana

Genomic testing will enjoy economies of scale



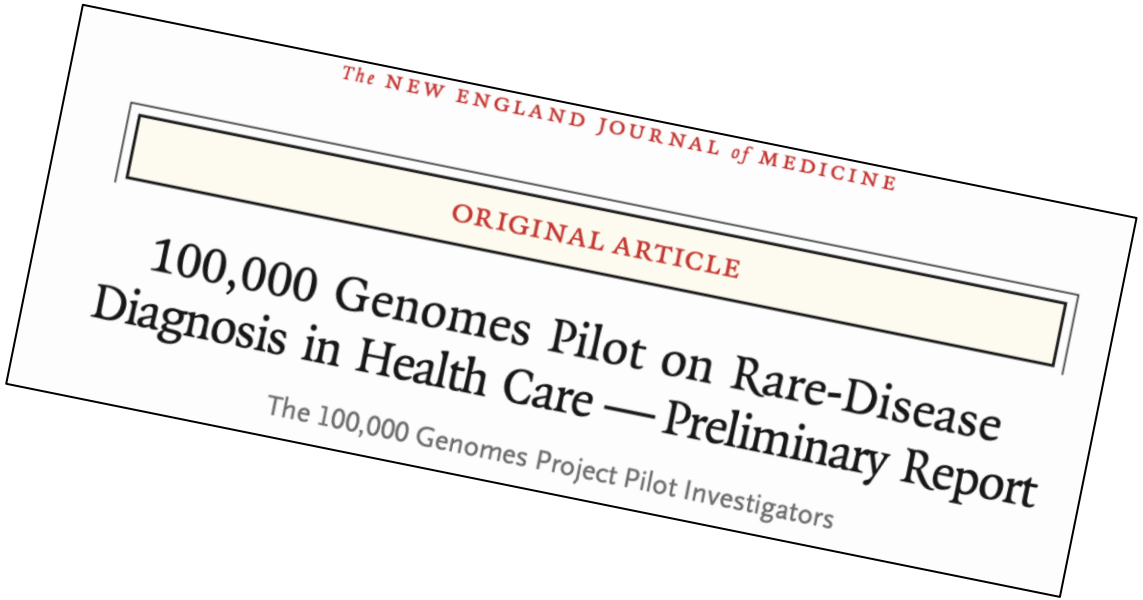
Schwarz K 2020

Helsana

Genomics England 100,000 Genomes Project

New diagnosis for
25% of participants.

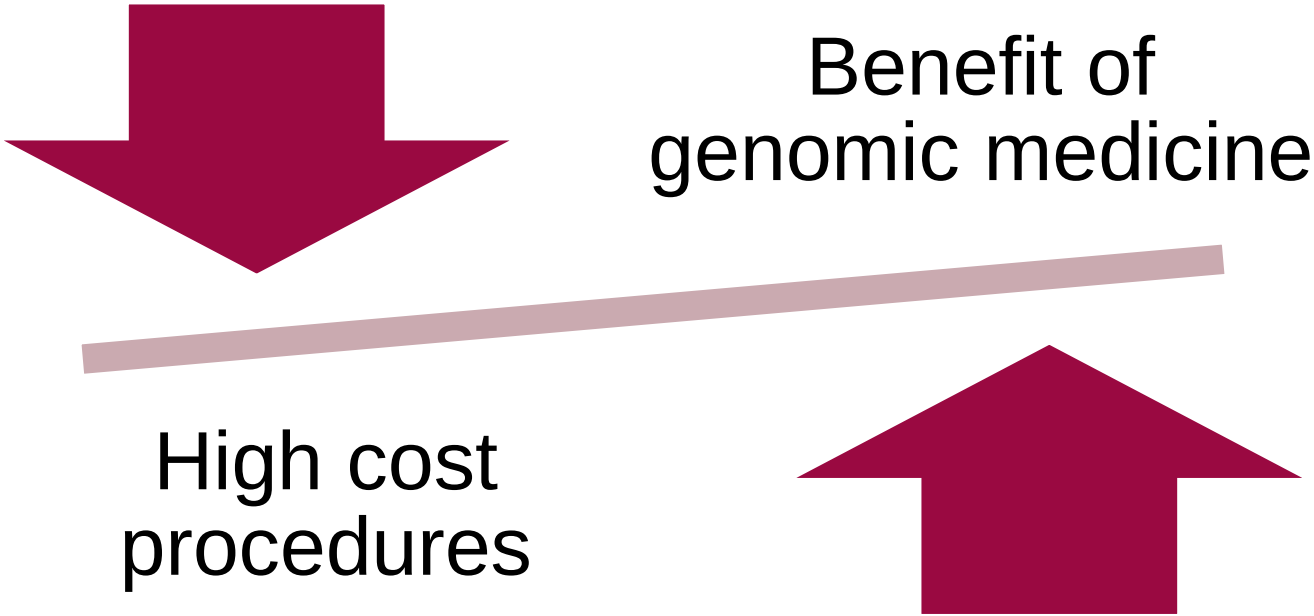
14% of these were found that would be missed by other conventional methods.



NEJM 2021

Helsana

Impact on cost-effectiveness



How genomic medicine can help payors

Running the business

- Cost optimization
- Better procurement
- Safer healthcare
- …
- Better underwriting
- Better actuarian modelling

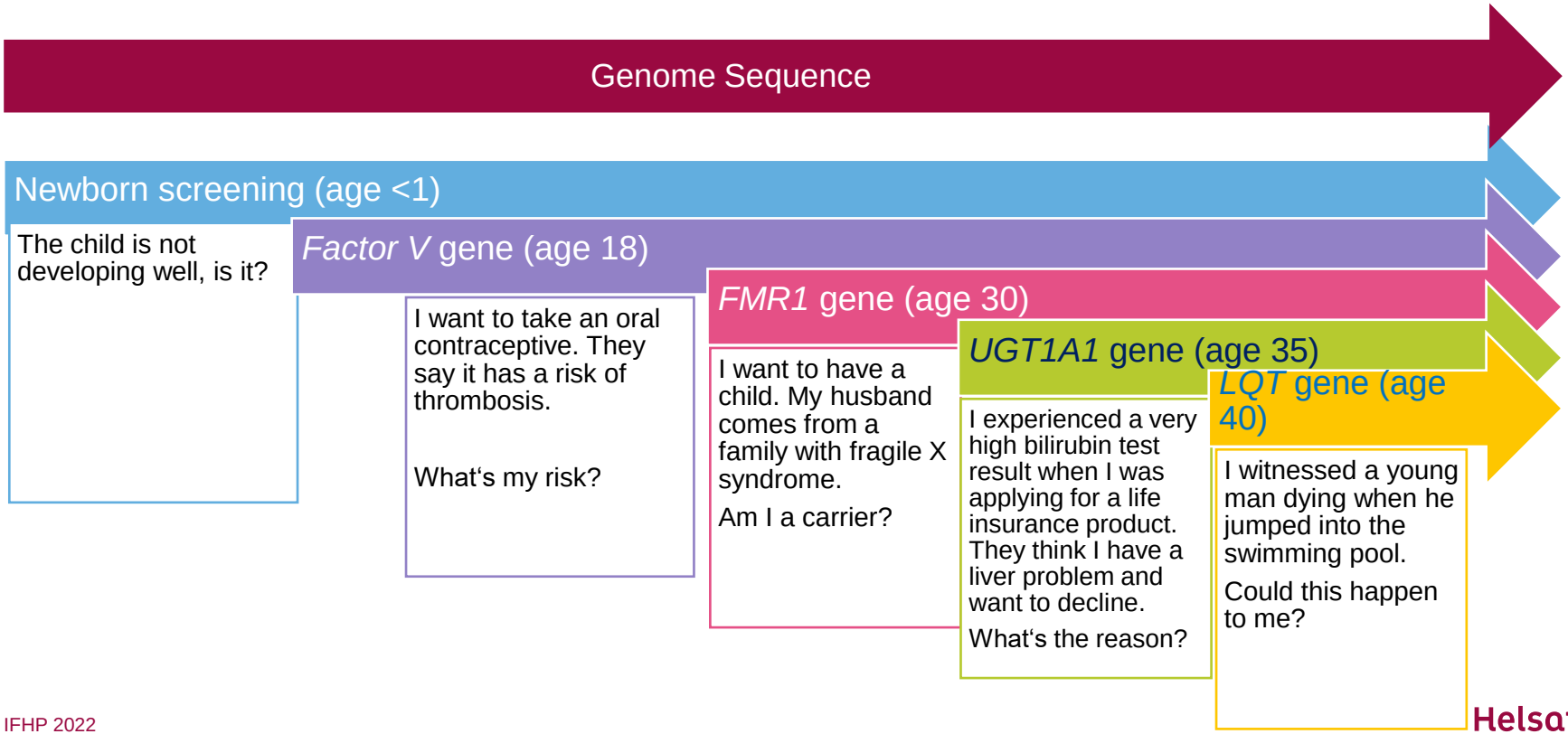
Changing the business

- New products
- Increasing customer loyality through better customer experience/journey
- …

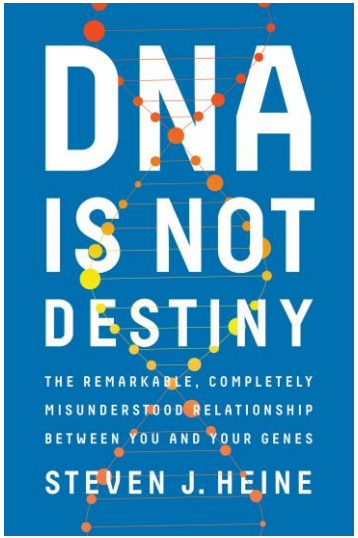
COULD THE GENOME BECOME A PERSONAL RESOURCE? A MINI EHR?

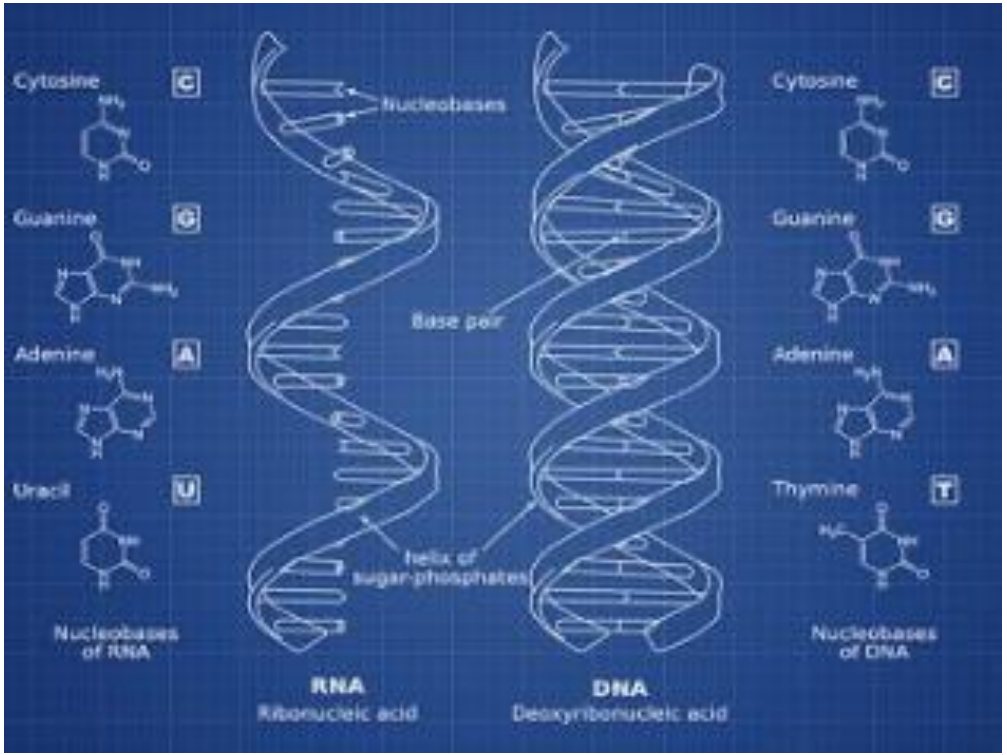
Helsana

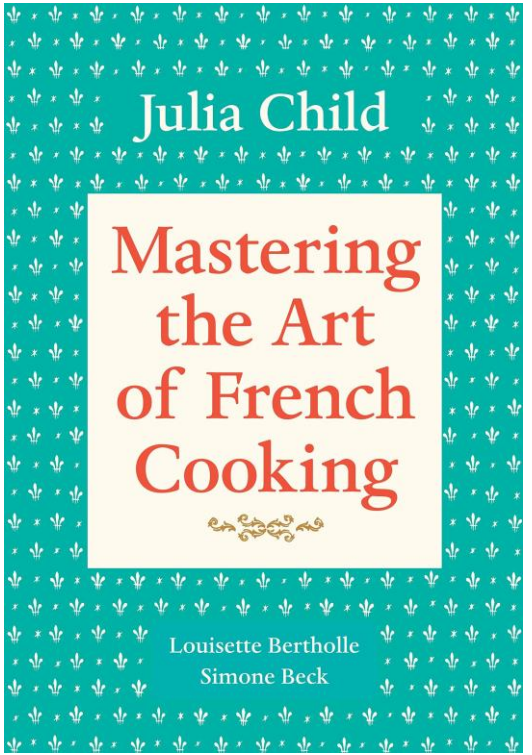
Read as you need – pay as you go
A real customer journey



Helsana


DNA
IS NOT
DESTINY
THE REMARKABLE, COMPLETELY
MISUNDERSTOOD RELATIONSHIP
BETWEEN YOU AND YOUR GENES
STEVEN J. HEINE


Cytosine
C
Guanine
G
Adenine
A
Uracil
U
Nucleobases of RNA
Nucleobases
Base pair
helix of sugar-phosphates
RNA
Ribonucleic acid
DNA
Deoxyribonucleic acid
Cytosine
C
Guanine
G
Adenine
A
Thymine
T
Nucleobases of DNA


Julia Child
Mastering the Art of French Cooking
Louisette Bertholle
Simone Beck

HELIBERNINA
HB-ZUS

Conclusions: Genomic medicine …

… has the potential to **optimise** healthcare.

… will assist to **better define** health and disease.

… will enable payors to **engineer new products** and redesign processes.

… will require all to understand that the industrial logic of healthcare will **move away from standardisation**.

… will make us better payors!

Thank you for your attention

Thomas D. Szucs

Chairman

Helsana

Committed to life.