유전체 기술을 이용한 심혈관 질환 진단방법

2019. 12. 14.

전성원 (Sungwon Jeon)

KOGIC, UNIST, South Korea

KOGIC
KOrean Genomics Industrialization and Commercialization Center
게놈산업기술센터

#JCR2019
#Healing Heart symposium

UNIST
울산과학기술원
ULSAN NATIONAL INSTITUTE OF SCIENCE AND TECHNOLOGY

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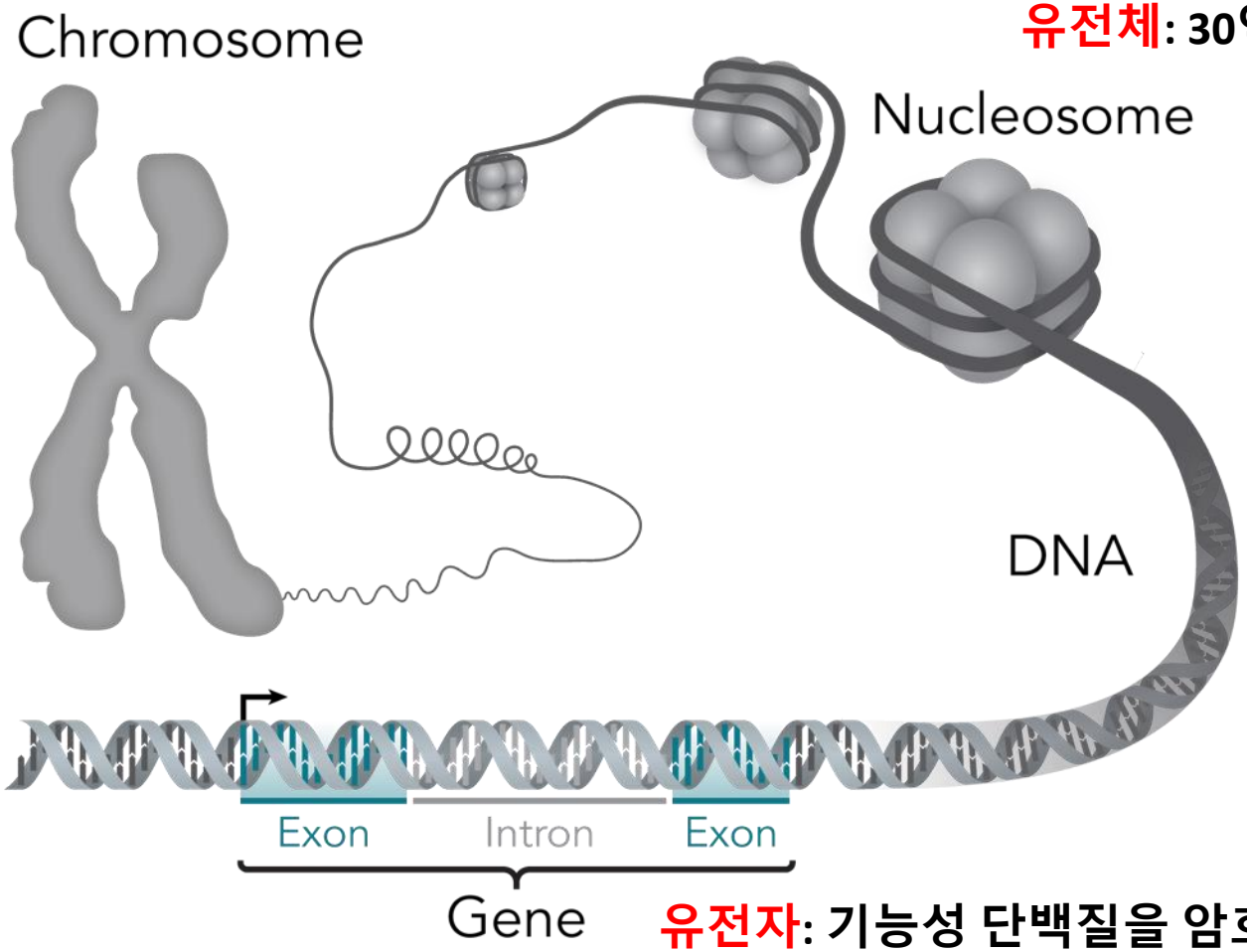
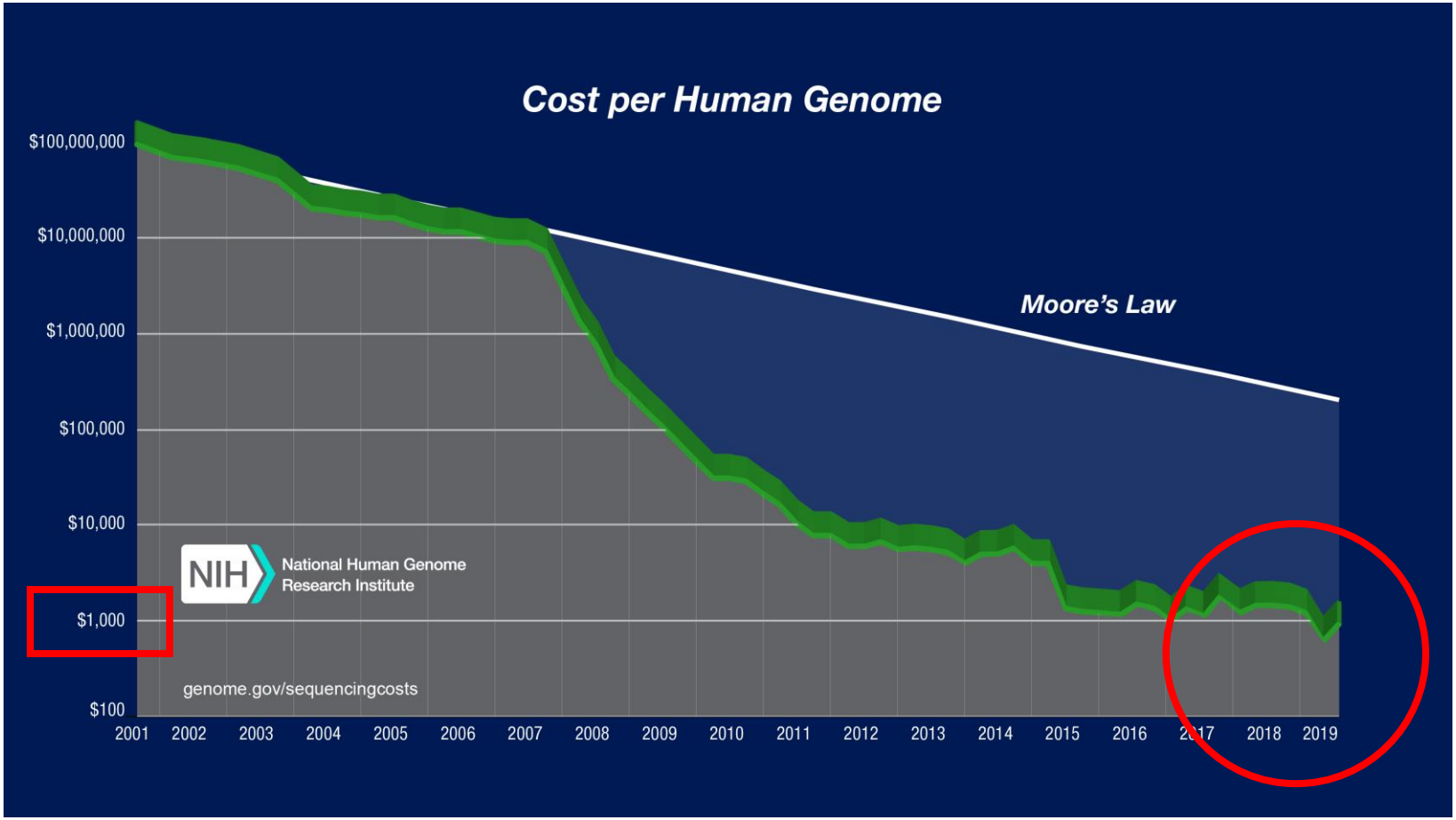
인간 게놈



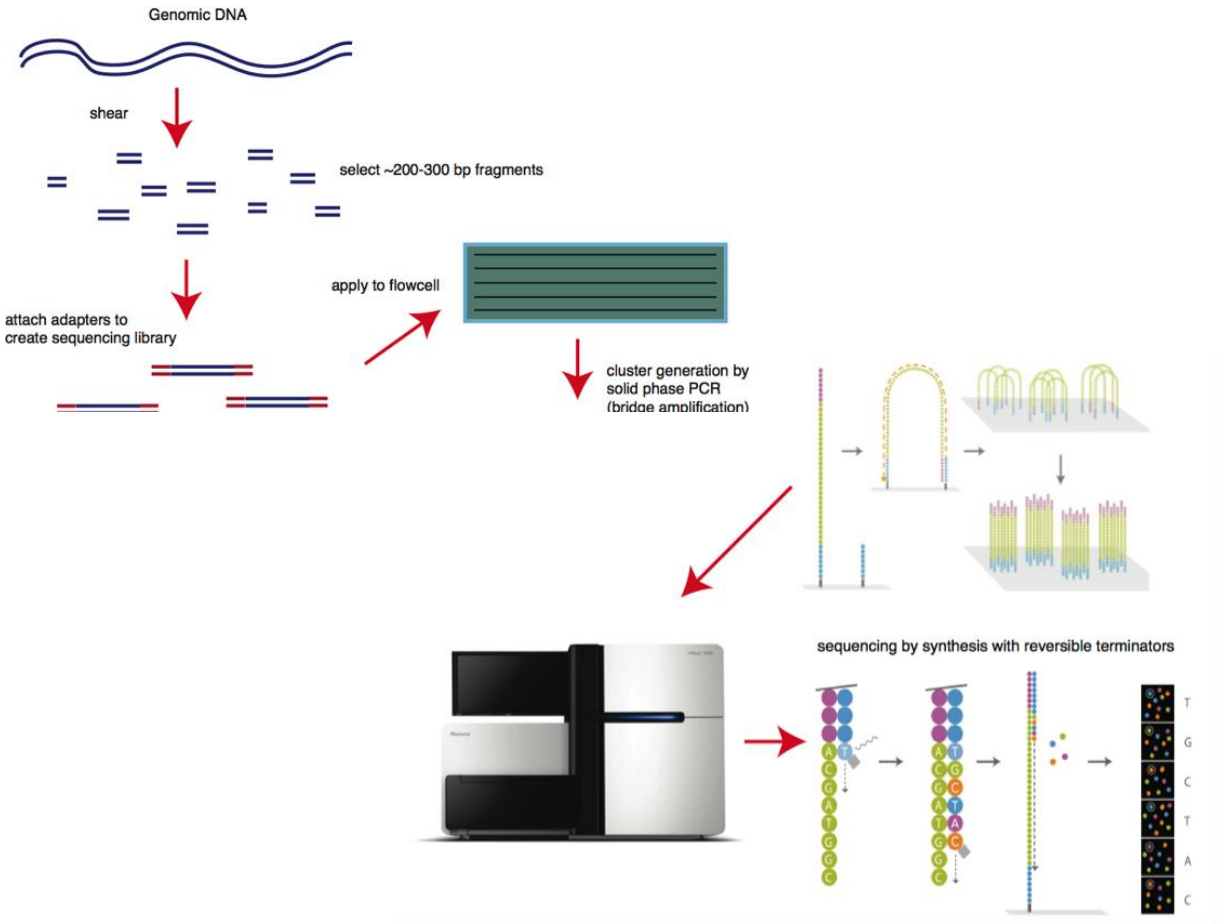
유전체: 30억 염기 서열 (사람경우)

유전자: 기능성 단백질을 암호화 하는 영역 (2만개)

Human whole genome sequencing cost

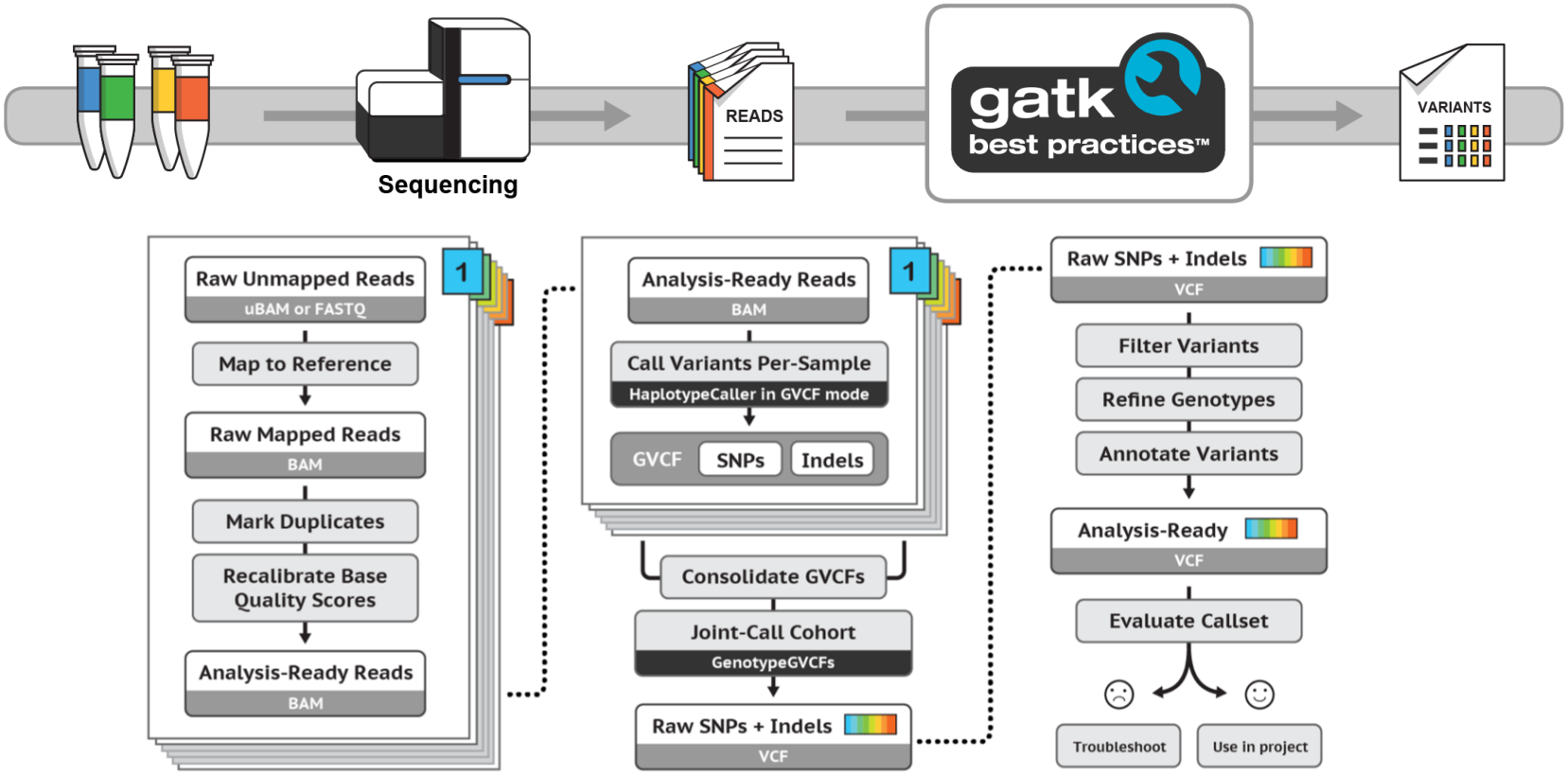


Next generation sequencing (NGS)



Bioinformatics (생정보학)

인간 게놈 분석 Pipeline



36 threads => 36 hours

https://software.broadinstitute.org/gatk/

https://www.intel.com/content/www/us/en/healthcare-it/solutions/documents/deploying-gatk-best-practices-paper.html

Human whole genome sequencing

Human genome sequencing data

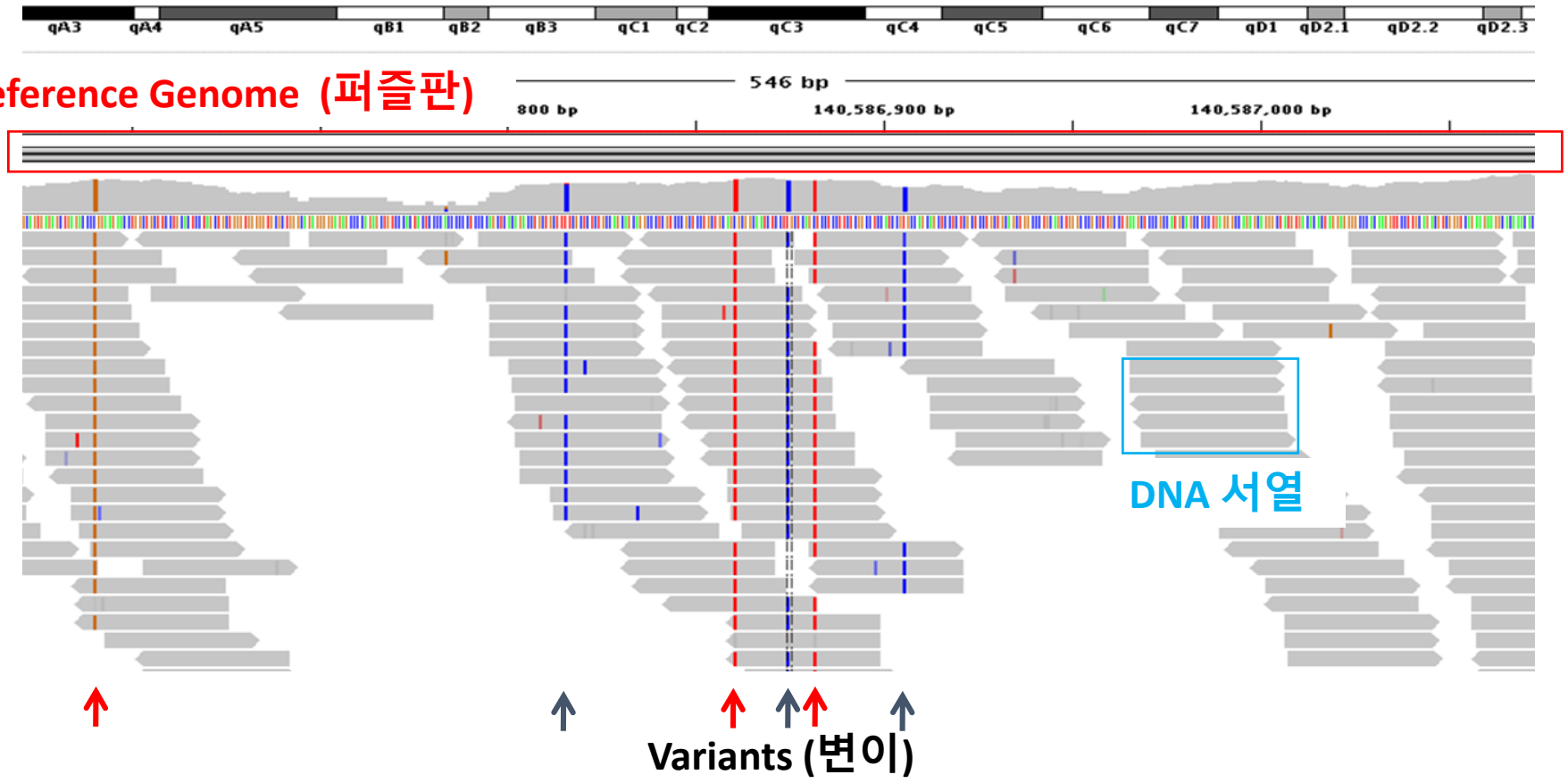
3Gb X 30배수 = 90Gb

생정보 기초분석 이후

0.5~1TB/sample

인간 게놈 분석

유전체: 30억 염기 서열 (사람경우)

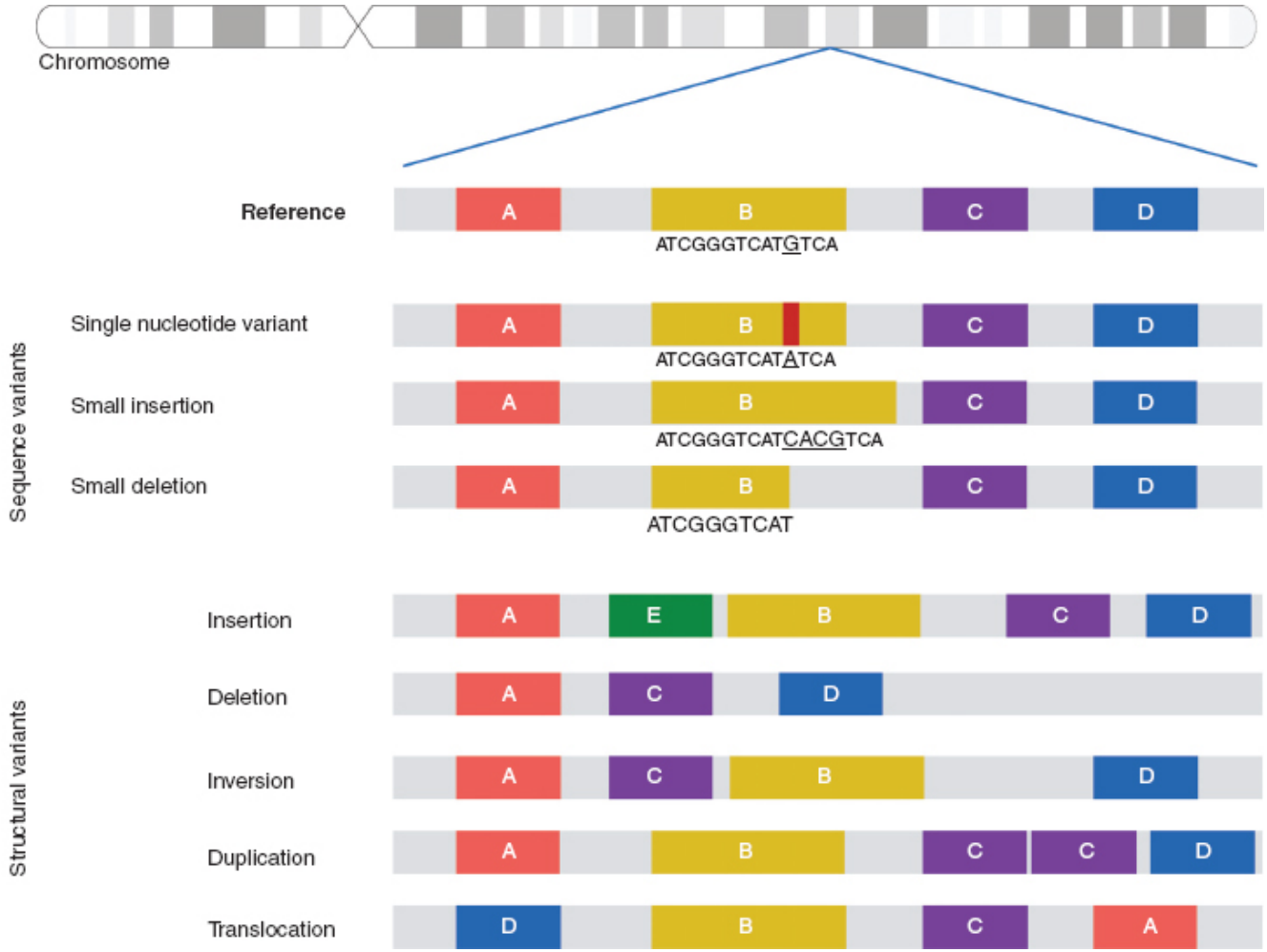


변이: 표준 서열과 다른 염기 서열
변이체: 총 변이의 합

보통 30X 정도는 해야한다.

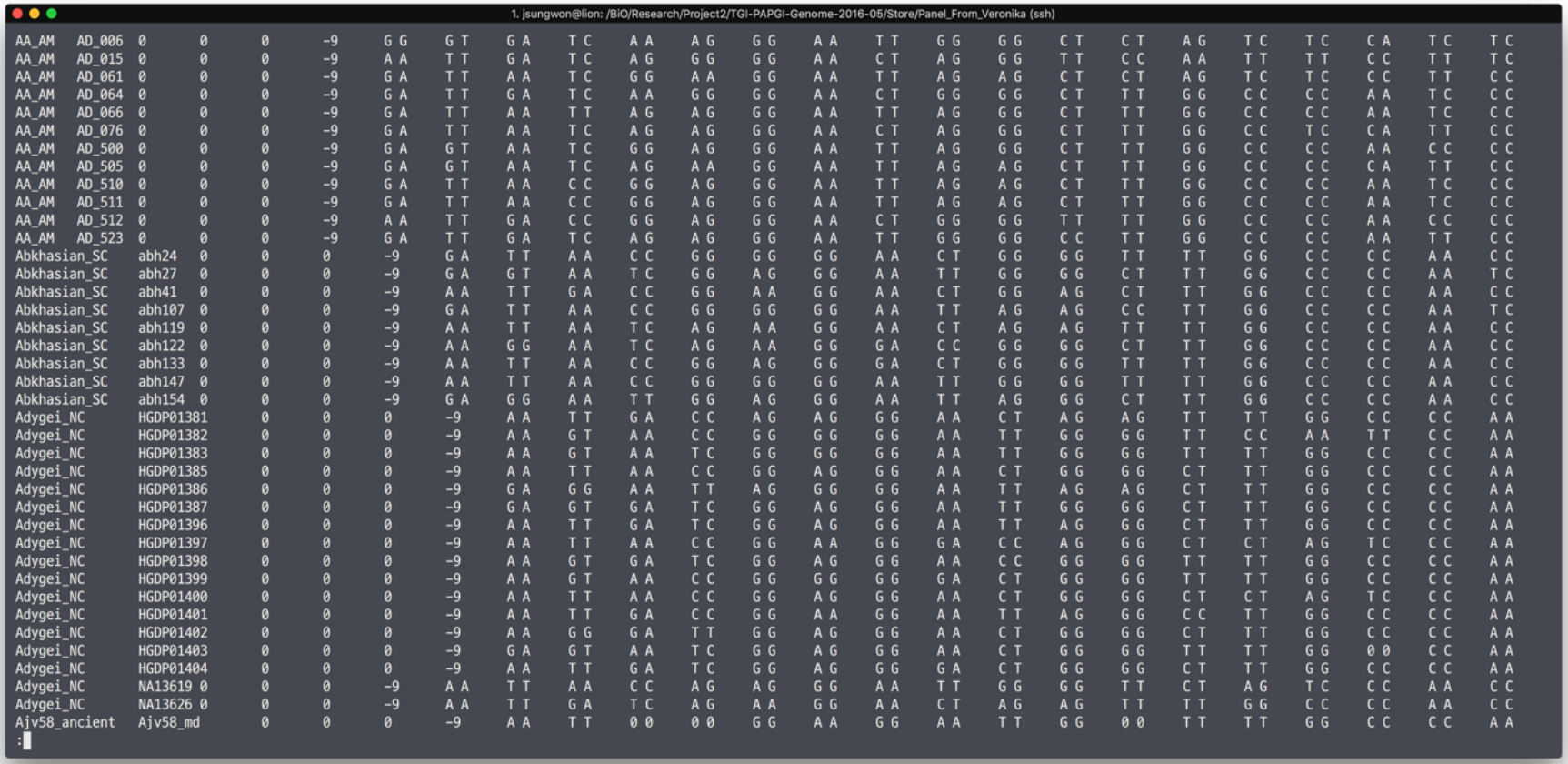
게놈 변이

https://neupsykey.com/genetics-3/



Variome (변이체)

샘플



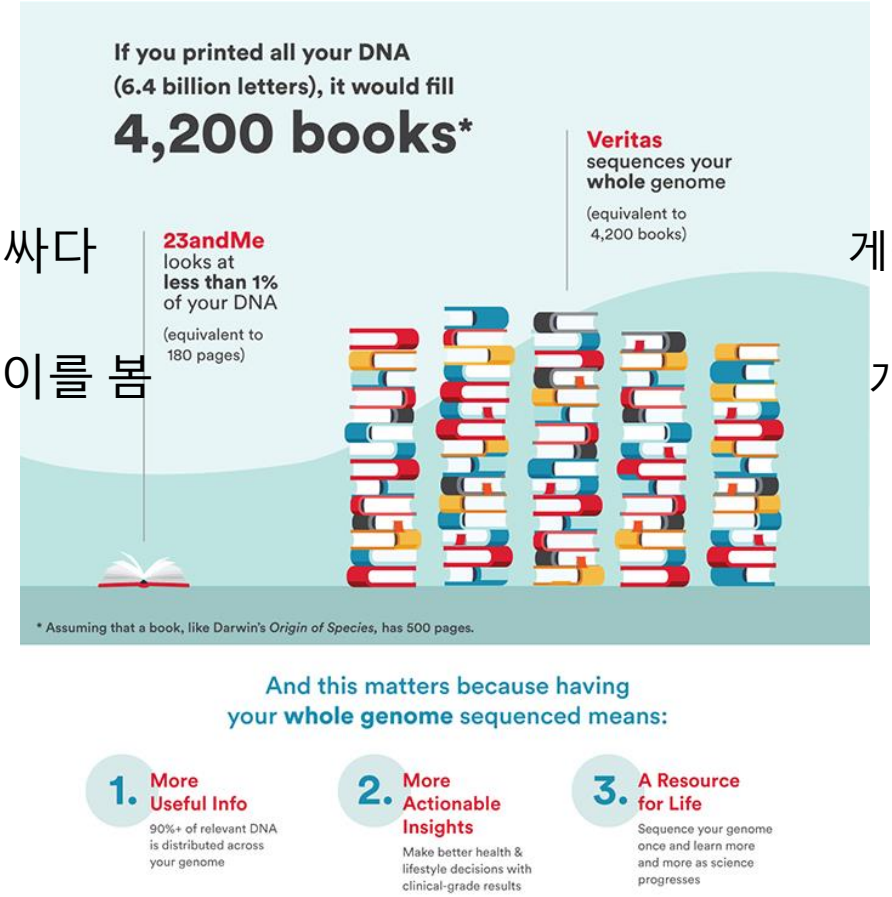
변이 정보

DNA Chip vs Whole genome sequencing (WGS)

DNA chip

가격이 상대적으로 싸다

대체로 Common 변이를 봄



WGS

게놈전체에 대한 변이 파악가능

개인 특이적인 변이도 발견가능

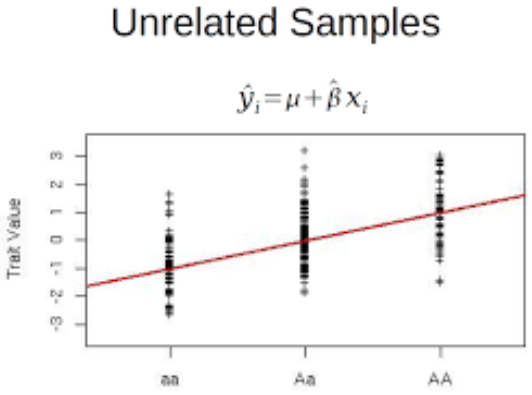
https://www.veritasgenetics.com/whats-difference-between-genetic-testing-technologies

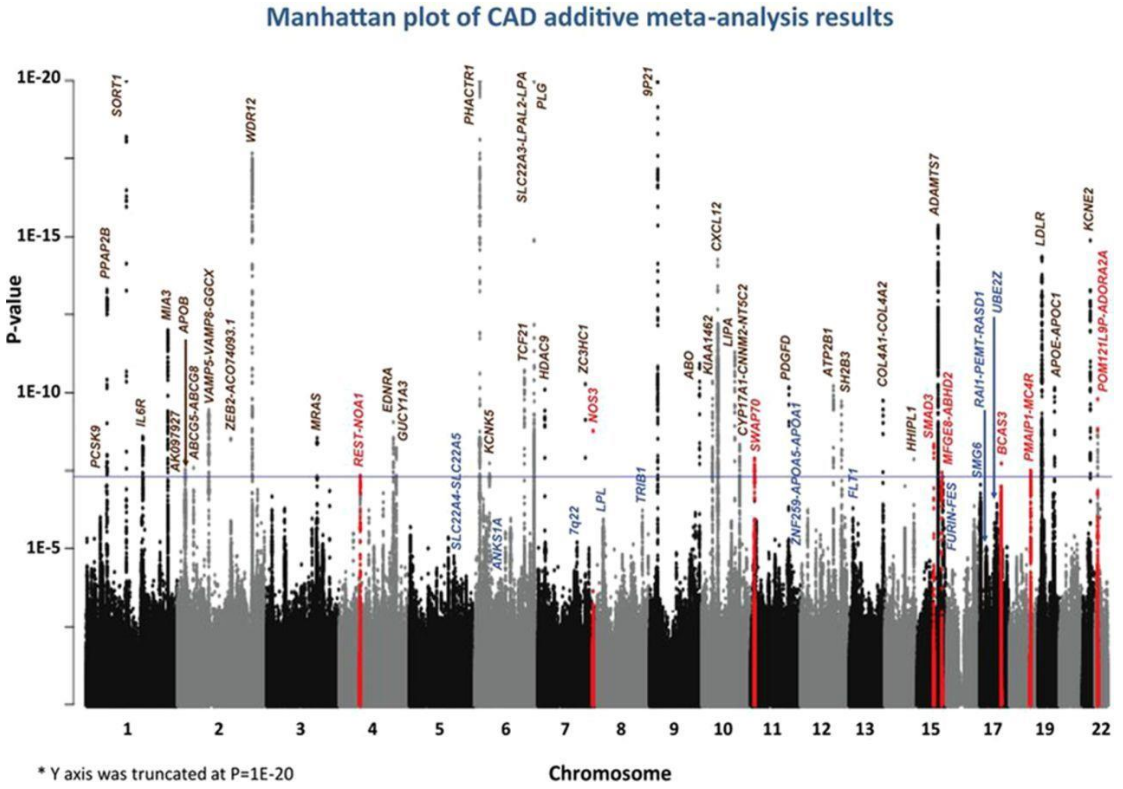
유전체기술로 심혈관질환 연구

예측?

진단?

Genome wide association study (GWAS)

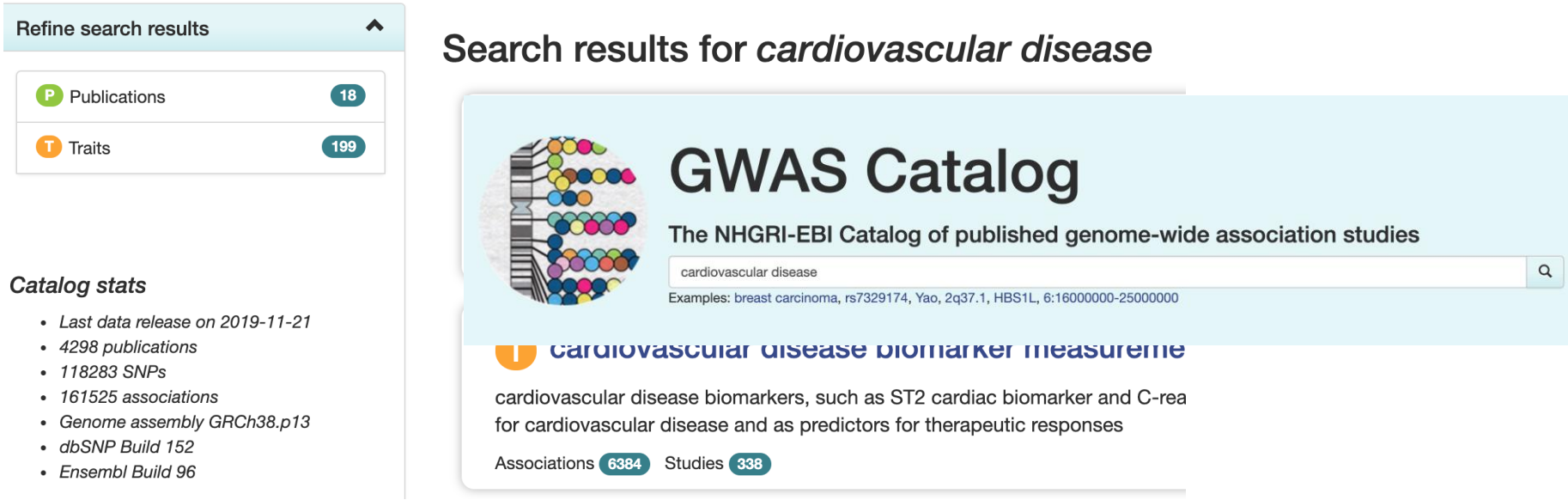




관련있는 변이 발견

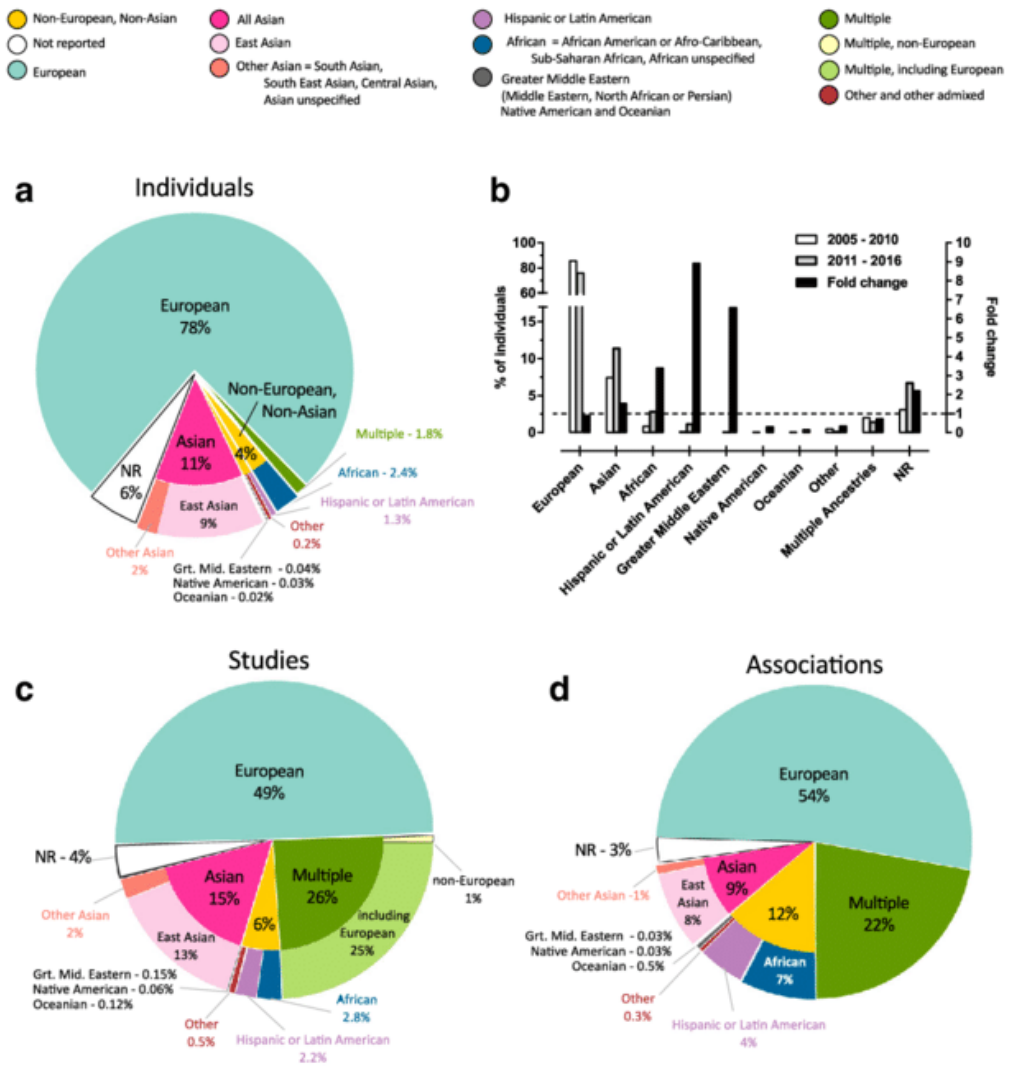
McPherson, Ruth, and Anne Tybjaerg-Hansen. "Genetics of coronary artery disease." *Circulation research* 118.4 (2016): 564-578.

CVD GWAS catalog variants



4,298 publications, 118,282 SNPs from GWAS catalog

Skewed population distribution



한국인, 아시아인 연구의 부족

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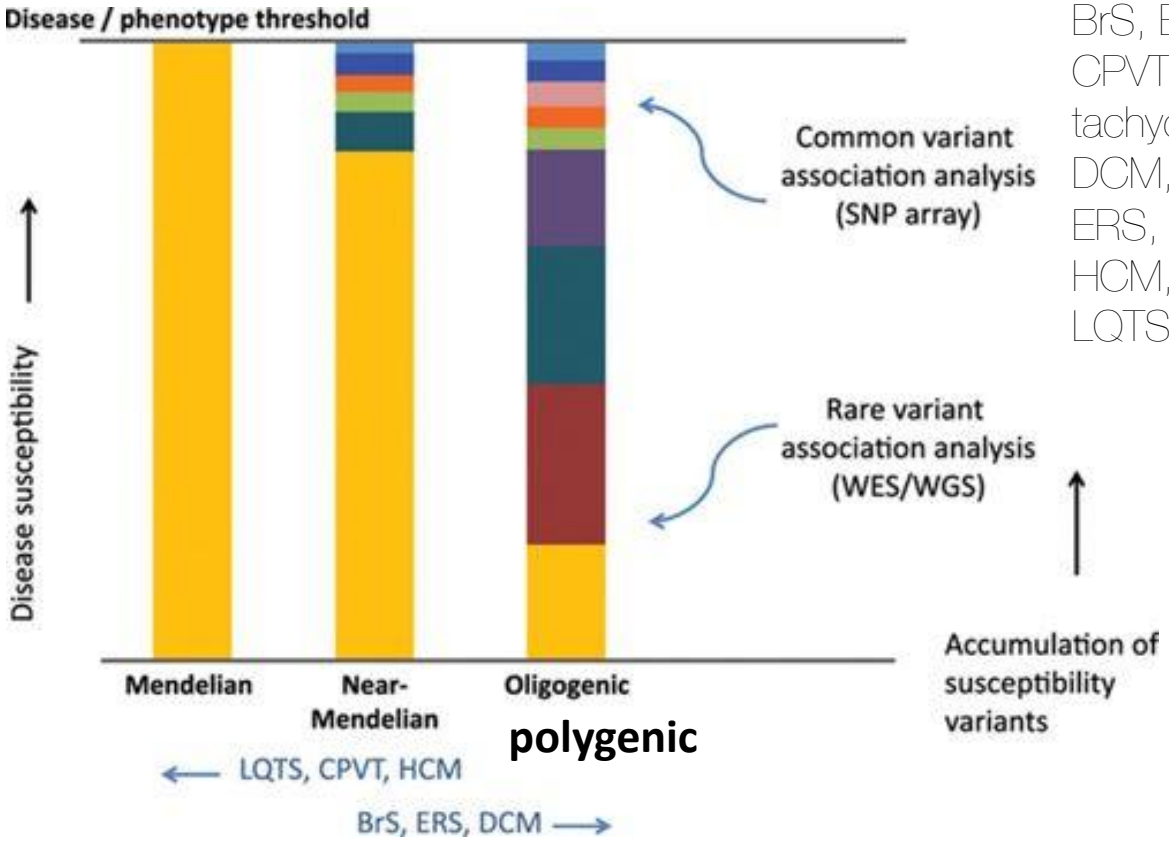
Morales, Joannella, et al. "A standardized framework for representation of ancestry data in genomics studies, with application to the NHGRI-EBI GWAS Catalog." *Genome biology* 19.1 (2018): 21.

Monogenic vs polygenic

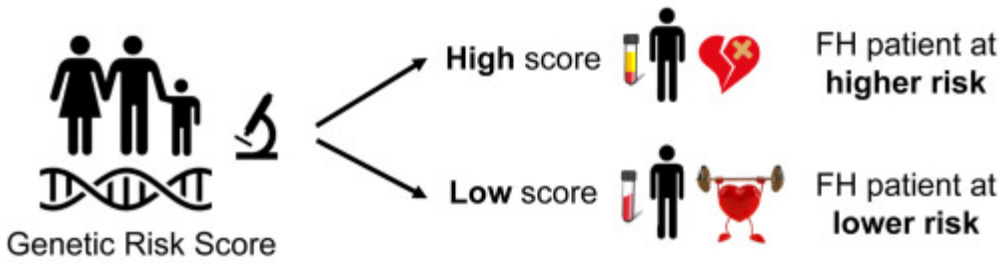
Bezzina, Connie R., Najim Lahrouchi, and Silvia G. Priori. "Genetics of sudden cardiac death." *Circulation research* 116.12 (2015): 1919-1936.



BrS, Brugada syndrome
CPVT, catecholaminergic polymorphic ventric
tachycardia
DCM, dilated cardiomyopathy
ERS, early repolarization syndrome
HCM, hypertrophic cardiomyopathy
LQTS, long-QT syndrome

Polygenic (genetic) risk score

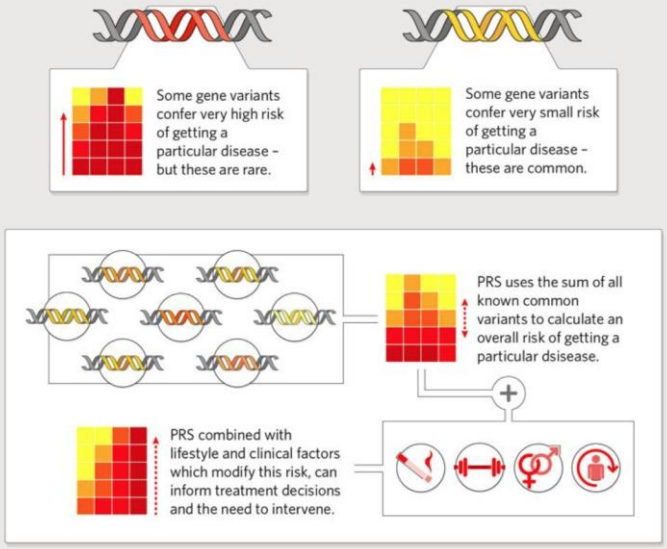
$$\hat{S} = \sum_{j=1}^{m} X_j \hat{\beta}_j,$$



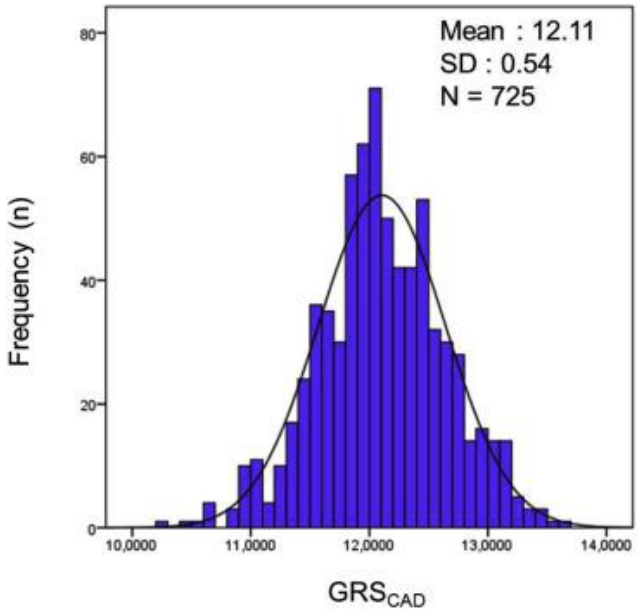
CLINICAL APPLICATION OF PRS

A polygenic risk score (PRS) is calculated from many small genetic variants, and can often be modified by lifestyle factors.

https://www.nature.com/articles/d42473-019-00270-w



Polygenic factors can influence the FH phenotype



Paquette, Martine, et al. "Polygenic risk score predicts prevalence of cardiovascular disease in patients with familial hypercholesterolemia." *Journal of clinical lipidology* 11.3 (2017): 725-732.

AI for CVD Risk prediction

RESEARCH ARTICLE

Cardiovascular disease risk prediction using automated machine learning: A prospective study of 423,604 UK Biobank participants

Ahmed M. Alaa[1]*, Thomas Bolton[2,3], Emanuele Di Angelantonio[2,3], James H. F. Rudd[4], Mihaela van der Schaar[1,5,6]

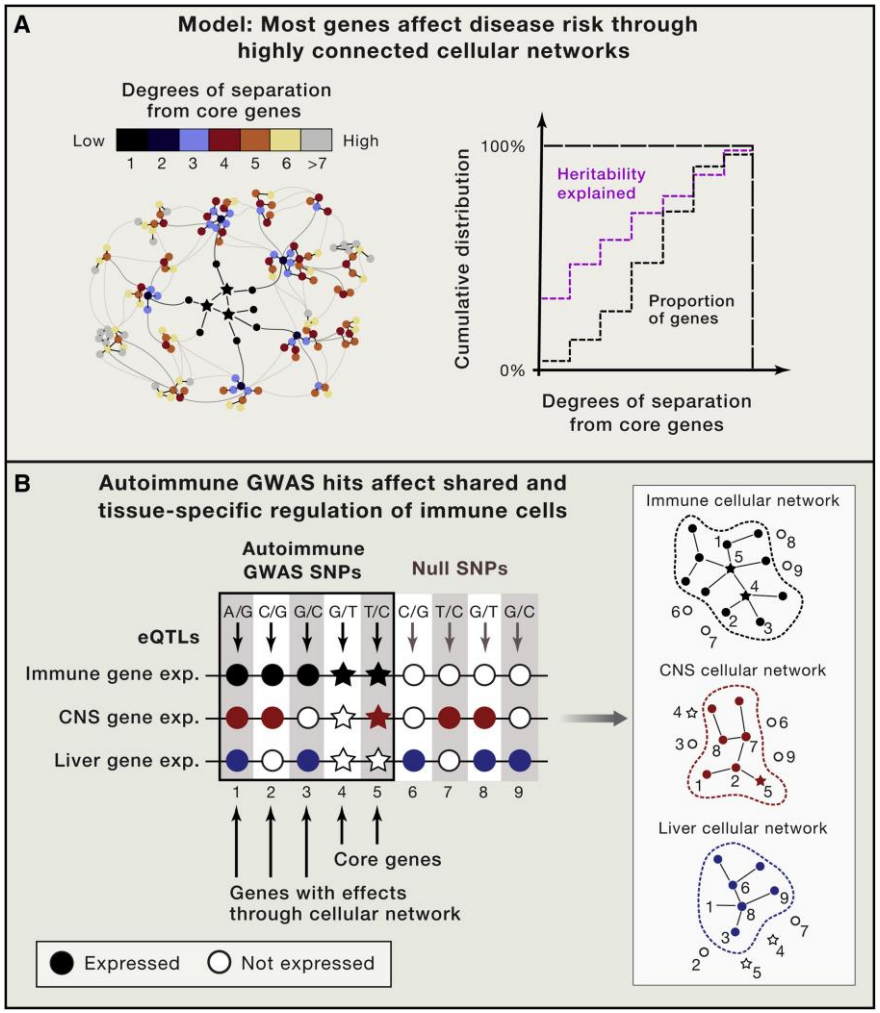
1 University of California Los Angeles, Los Angeles, California, United States of America, **2** Department of Public Health and Primary Care, University of Cambridge, Cambridge, United Kingdom, **3** National Institute for Health Research (NIHR) Blood and Transplant Research Unit (BTRU) in Donor Health and Genomics, University of Cambridge, Cambridge, United Kingdom, **4** Department of Cardiovascular Medicine, University of Cambridge and Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom, **5** University of Oxford, Oxford, United Kingdom, **6** Alan Turing Institute, London, United Kingdom

* ahmedmalaa@ucla.edu

Model	AUC-ROC	Absolute AUC-ROC Change
Framingham Score	0.724 ± 0.004	Baseline model
Cox PH Model (7 core variables)	0.734 ± 0.005	+ 1.0%
Cox PH Model (all variables)	0.758 ± 0.005	+ 3.4%
Support Vector Machines	0.709 ± 0.061	- 1.5%
Random Forest	0.730 ± 0.004	+ 0.6%
Neural Networks	0.755 ± 0.005	+ 3.1%
AdaBoost	0.759 ± 0.004	+ 3.5%
Gradient Boosting	0.769 ± 0.005	+ 4.5%
AutoPrognosis (7 core variables)	0.744 ± 0.005	+ 2.0%
AutoPrognosis (369 non-lab. variables)	0.761 ± 0.005	+ 3.7%
AutoPrognosis (104 lab. variables)	0.735 ± 0.008	+ 1.1%
AutoPrognosis (all variables)	0.774 ± 0.005	+ 5.0%

Omnigenic model

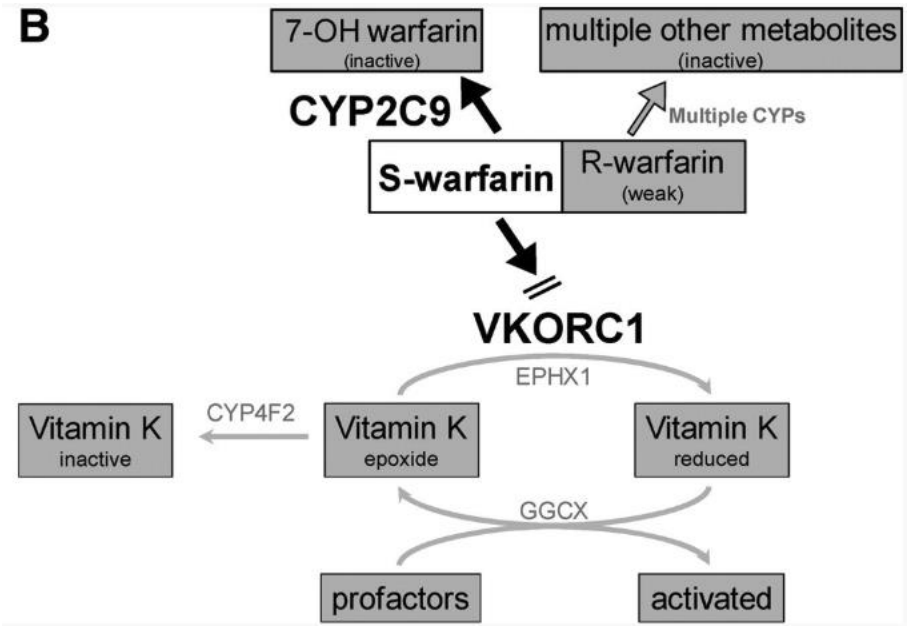
Boyle, Evan A., Yang I. Li, and Jonathan K. Pritchard. "An expanded view of complex traits: from polygenic to omnigenic." *Cell* 169.7 (2017): 1177-1186.



We propose that gene regulatory networks are sufficiently interconnected such that all genes expressed in disease-relevant cells are liable to affect the functions of core disease-related genes and that most heritability can be explained by effects on genes outside core pathways.

무한히 많은 작은 효과들

Pharmacogenomics : Warfarin

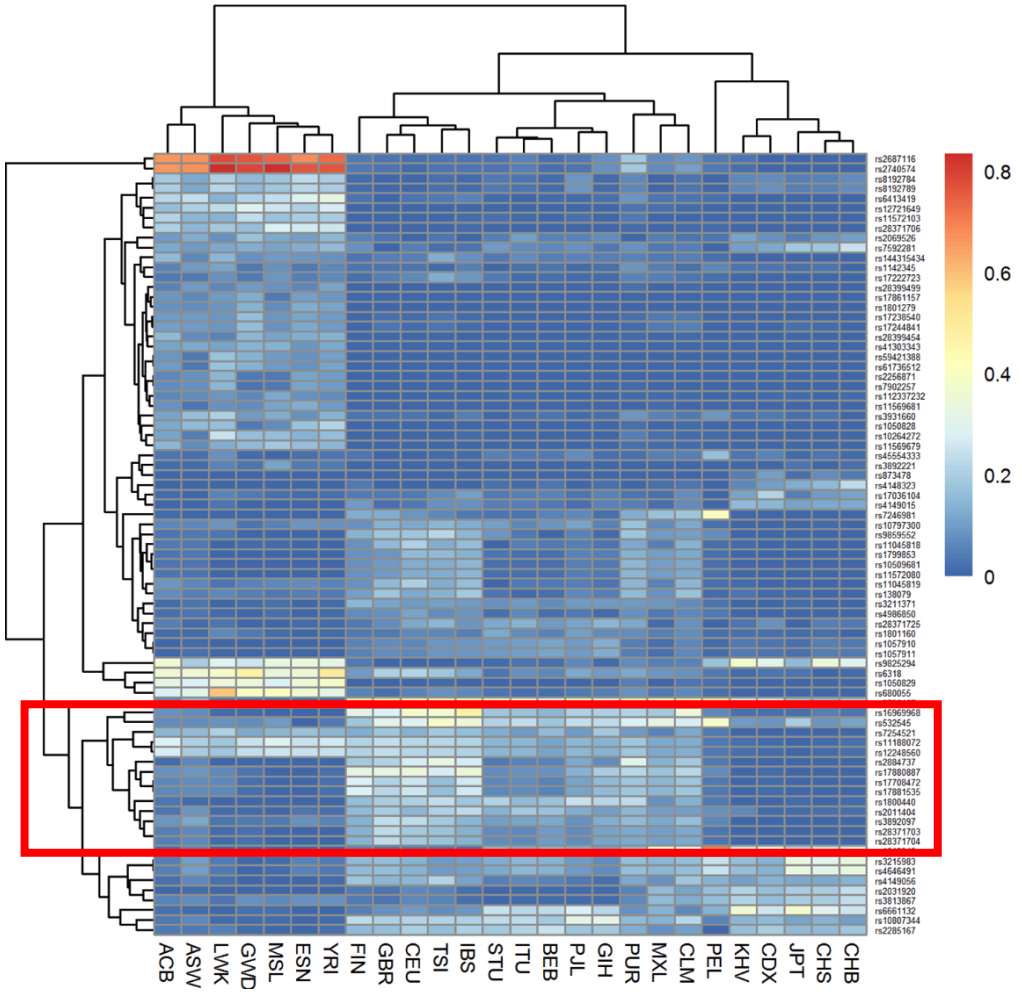


variants in CYP2C9 and VKORC1 contribute to variable warfarin dosage.

Roden, Dan M., et al. "Cardiovascular pharmacogenomics." *Circulation research* 109.7 (2011): 807-820.

Pharmacogenomics

인종마다 변이의
빈도가 차이남



아프리카 유럽 아메리카 동아시아

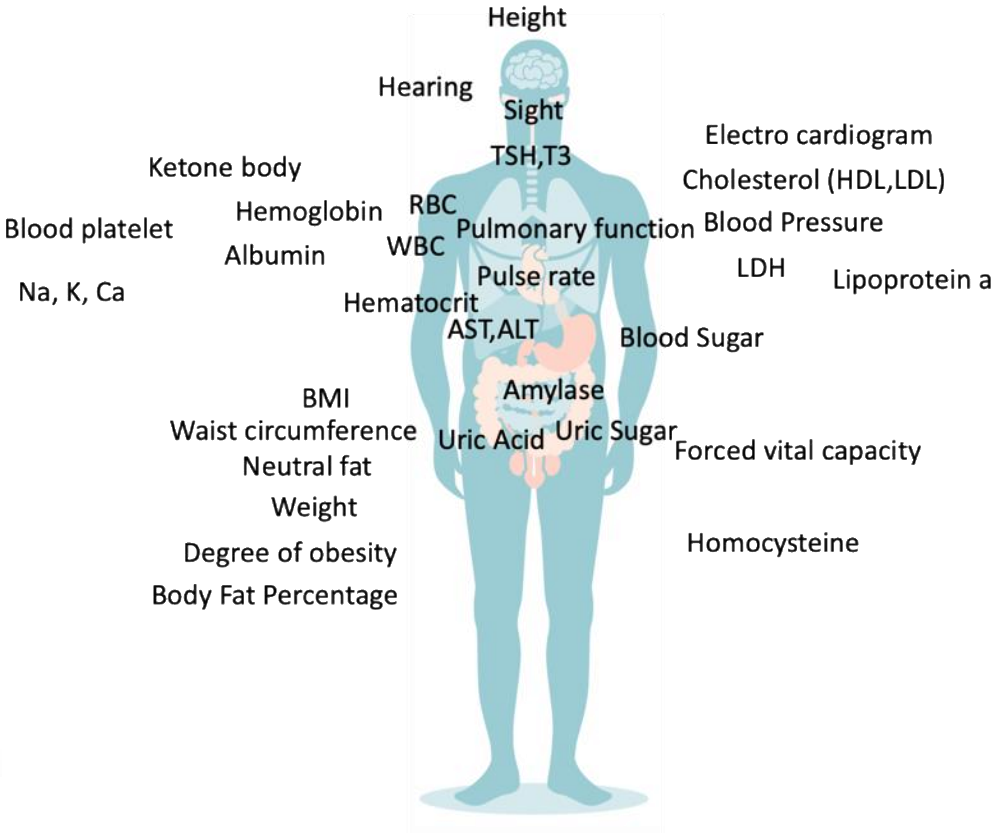
Minor Allele Frequency heatmap for 79 Pharmacogenomics variants that are common (MAF> = 0.1) and rare (MAF< = 0.005) in at least one 1KG population.

Lakiotaki, Kleanthi, et al. "Exploring public genomics data for population pharmacogenomics." *PloS one* 12.8 (2017): e0182138.

Korean genome database

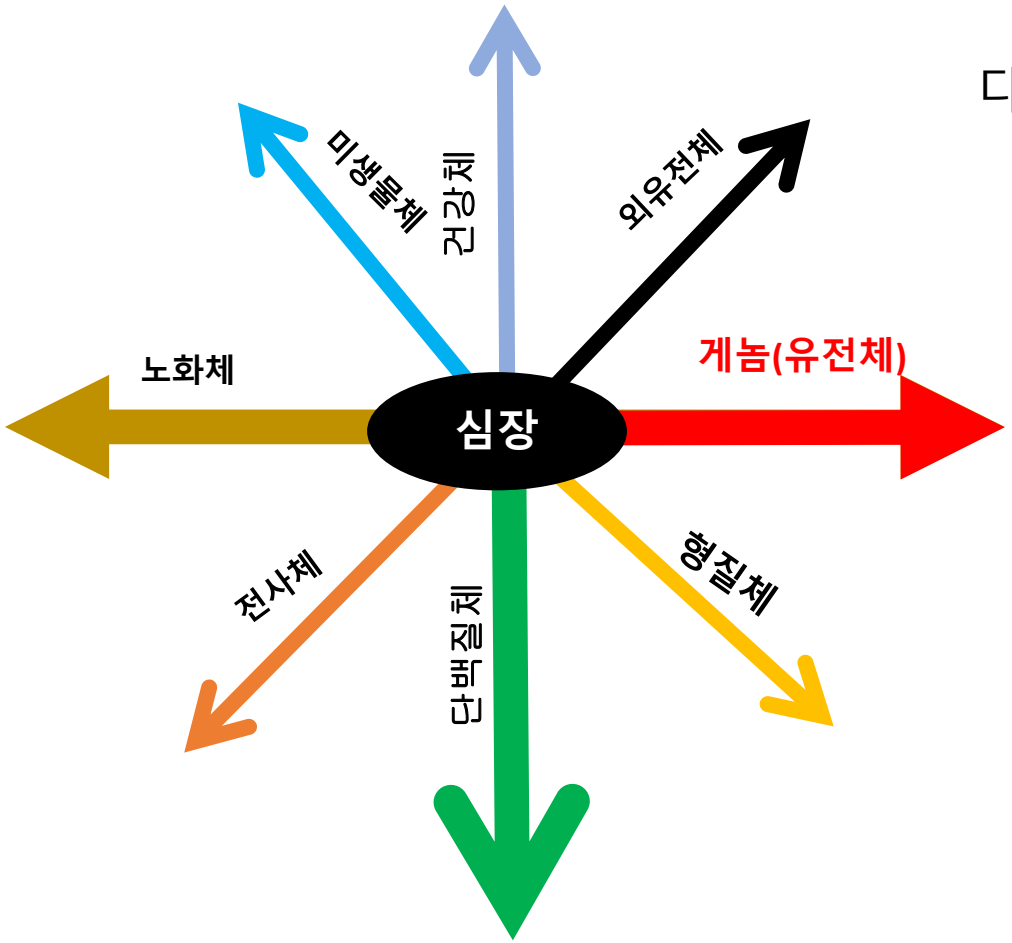
울산 만명게놈 프로젝트

국민 게놈



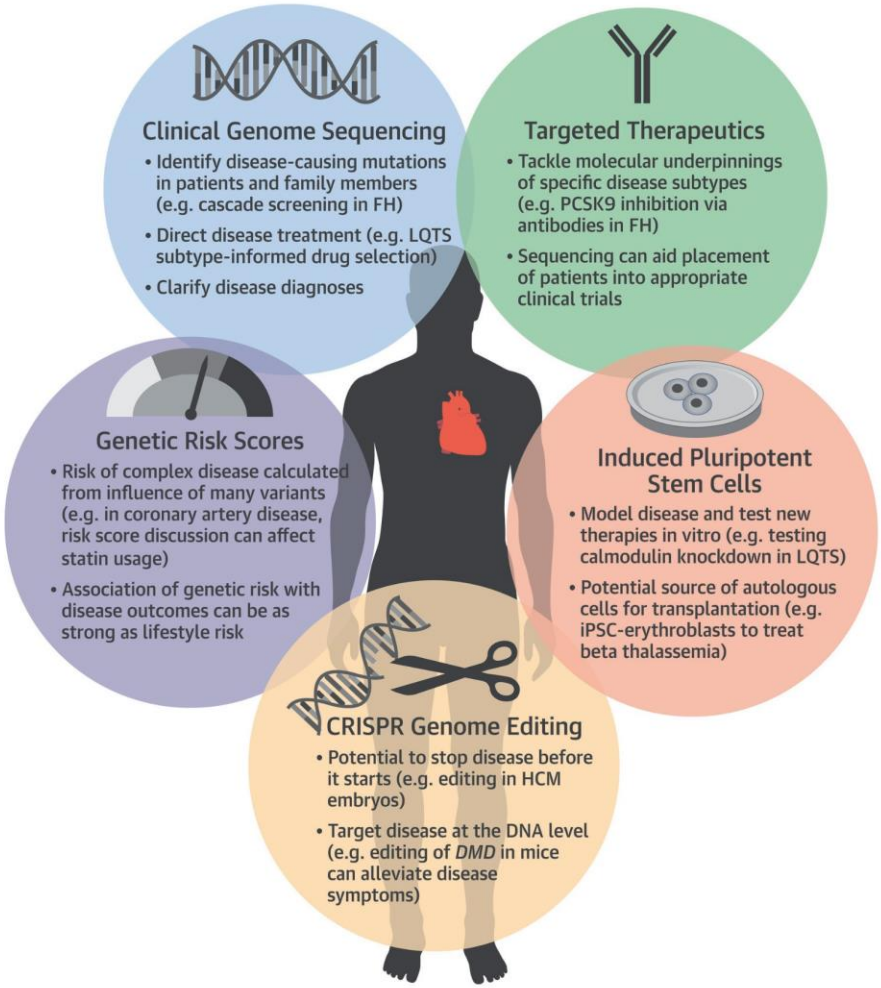
건강 검진 정보

Multi-omics



다중 오믹스를 통한 심장게놈 연구

Precision/Personalized medicine



개인 게놈 정보를
활용한
정밀/맞춤의학

Dainis, Alexandra M., and Euan A. Ashley. "Cardiovascular precision medicine in the genomics era." *JACC: Basic to Translational Science* 3.2 (2018): 313-326.