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Kunnskap for en bedre verden

Clinical implications of population based genetic discoveries

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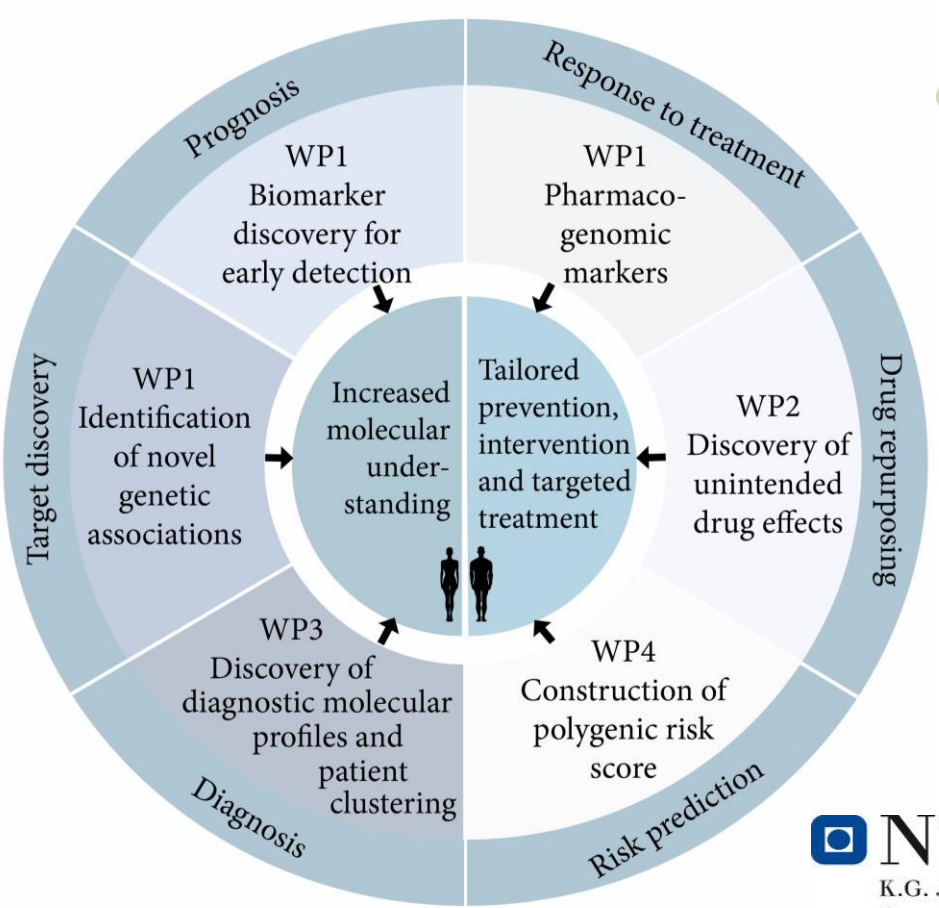
From populations to the clinic

WP 1 - Targeted follow-up of drug discovery

WP2 - Identify modifiable causes of disease

WP3 - Identifying molecular signatures of disease

WP4 – From genetic discovery to clinical translation



Courtesy of Ele Zeggini

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The HUNT study

1984-86 | 1995-97 | 2006-08 | 2017-19

HUNT1 (20yrs+)
77 200 (89%)

HUNT2 (20yrs+)
65 200 (70%)

HUNT3 (20yrs+)
50 800 (54%)

HUNT4 (20yrs+)
55 600 (54 %)

HUNT 70+ : 9000 included in a cognitive test program
90-99 yrs: 735
- **100 yrs: 18**
- **7000 have participated in all four HUNT-studies**

47 000 (H1-H2)
37 700 (H2-H3)
34 000 (H3-H4)
26 100 (H2-H4)
19 000 (H1-H4)

Collecting disease endpoints by linkage to EHR and clinical diagnostic registries on a regional and national level

> 200 completed PhD-degrees, 100 peer review papers/year

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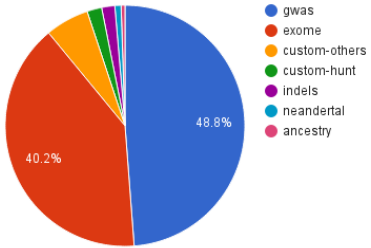
The HUNT genes all-in project

- Genome wide genotyping of 70 000 HUNT-participants (Human Core Exome), ~100 000 by June 2020
- WGS of 2200 – low pass
- 604 000 genetic markers including 60 000 custom “HUNT SNPs”, imputed up till 28 mill (HRC/TopMed)
- CVD as main focus, > 60 sub-studies and 150 collaborating clinicians addressing other disease outcomes
- > 3000 GWAS-analyses completed
- Challenging ethics with actionable variants such as Familial Hypercholesterolemi (FH), BRCA2 related to return of results

Human Core Exome



CVD	Endo	Gastro	Lung	Neuro	Pharma	Kidney	Reuma	Infection	Women	Others
CVD main	Thyroid	IBD *	Asthma, KOLS	Psych. Disorders *	CVD-pharmaco-genomics-statins	CKD	AS	Sepsis	PCOS	Psoriasis
Afib *	BMD *	IBS *		Pain *	Anti-coagulants		RA		Endometriosis	Allergy
HT *	Vit D *	Reflux		Sleep *					Pre-eclampsia	Inflammation
VTE *	T2D *	CRC *		Head Ache					Gestational age	
FH *	LADA *			Parkinson *					Pelvic disorders	
Phys activity				Stroke *					Birth Weight	
Exercise *				Eating disorders *						
TnI *				Low back pain						
Arrythmia										
AAA *										
Liver *										

Our analytic environment (HUNT Cloud)

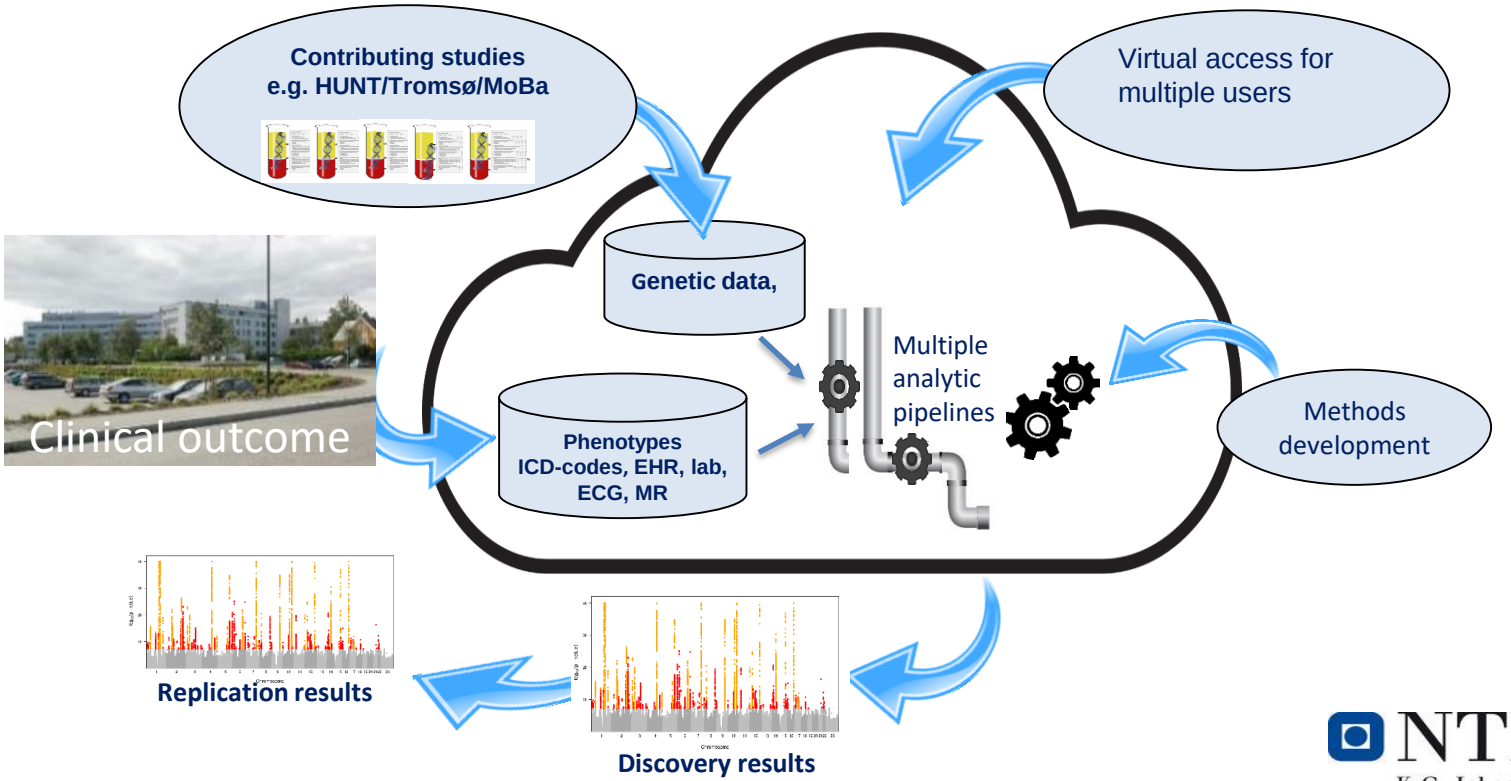


Illustration inspired by Brody JA, et al
Analysis commons, a team approach to discovery in a big-data environment for genetic epidemiology,
Nat Genet. Oct, 2017

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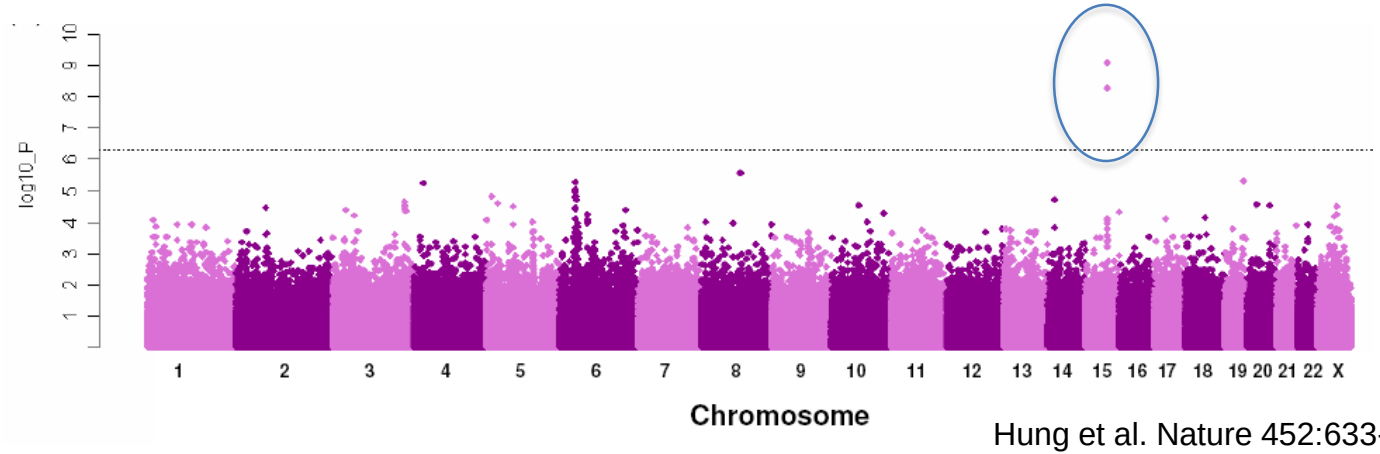
HUNT-involvement in biomarker discoveries

The first HUNT GWAS:

A susceptibility locus for lung cancer that maps to a nicotinic acetylcholine receptor subunit genes on 15q25



Hung et al. Nature 452:633-637 (2008)

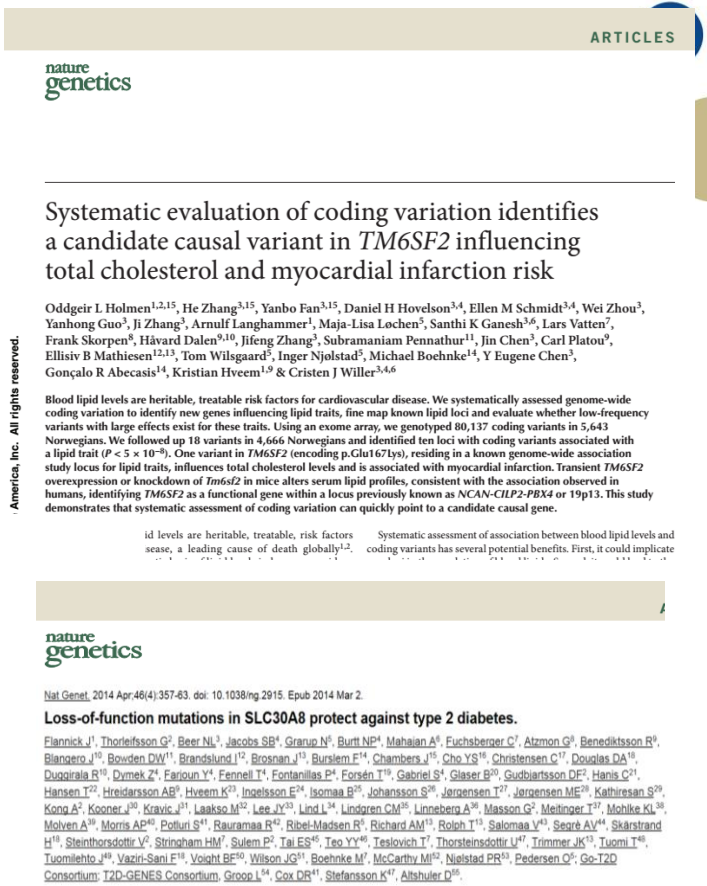
GWAS-analyses has later been conducted on > 3000 binary or quantitative traits based on > 7000 unique variables from HUNT Data bank and > 2000 ICD-codes retrieved from medical records

Protective gene against MI

- Exome array genotyping of ~ 80 000 coding variants in 5643 subjects from HUNT Biobank
- Identified a LoF causal variant in *TM6SF2* affecting lipid levels and risk of MI
- Replicated in 4666 participants from the Tromsø study, 10 variants confirmed to be associated with a lipid trait p< $5x10^{-8}$
- Transient overexpression or knockdown in a mouse models altered serum lipid profiles
- *TM6SF2* has also shown an increased risk of fatty liver disease and T2D, so not likely to be the best drug target

Protective gene against type 2 diabetes

- 150 000 across 5 ancestry groups, 6000 from HUNT
- 12 variants in *SLC30A8*
- A common protein truncating variant (p. Trp325Arg) was assoc. with risk of T2D, glucose and proinsulin levels
- Carriers had a 65% reduced T2D risk



ARTICLES

nature genetics

Systematic evaluation of coding variation identifies a candidate causal variant in *TM6SF2* influencing total cholesterol and myocardial infarction risk

Oddgeir L Holmen[1,2,15], He Zhang[3,15], Yanbo Fan[3,15], Daniel H Hovelson[3,4], Ellen M Schmidt[3,4], Wei Zhou[3], Yanhong Guo[3], Ji Zhang[3], Arnulf Langhammer[1], Maja-Lisa Løchen[5], Santhi K Ganesh[3,6], Lars Vatten[7], Frank Skorpen[8], Håvard Dalen[9,10], Jifeng Zhang[3], Subramaniam Pennathur[11], Jin Chen[3], Carl Platou[9], Ellisiv B Mathiesen[12,13], Tom Wilsgaard[5], Inger Njølstad[5], Michael Boehnke[14], Y Eugene Chen[3], Gonçalo R Abecasis[14], Kristian Hveem[1,9] & Cristen J Willer[3,4,6]

Blood lipid levels are heritable, treatable risk factors for cardiovascular disease. We systematically assessed genome-wide coding variation to identify new genes influencing lipid traits, fine map known lipid loci and evaluate whether low-frequency variants with large effects exist for these traits. Using an exome array, we genotyped 80,137 coding variants in 5,643 Norwegians. We followed up 18 variants in 4,666 Norwegians and identified ten loci with coding variants associated with a lipid trait ($P < 5 \times 10^{-8}$). One variant in *TM6SF2* (encoding p.Glu167Lys), residing in a known genome-wide association study locus for lipid traits, influences total cholesterol levels and is associated with myocardial infarction. Transient *TM6SF2* overexpression or knockdown of *Tm6sf2* in mice alters serum lipid profiles, consistent with the association observed in humans, identifying *TM6SF2* as a functional gene within a locus previously known as *NCAN-CILP2-PBX4* or 19p13. This study demonstrates that systematic assessment of coding variation can quickly point to a candidate causal gene.

id levels are heritable, treatable, risk factors sease, a leading cause of death globally[1,2].

Systematic assessment of association between blood lipid levels and coding variants has several potential benefits. First, it could implicate

nature genetics

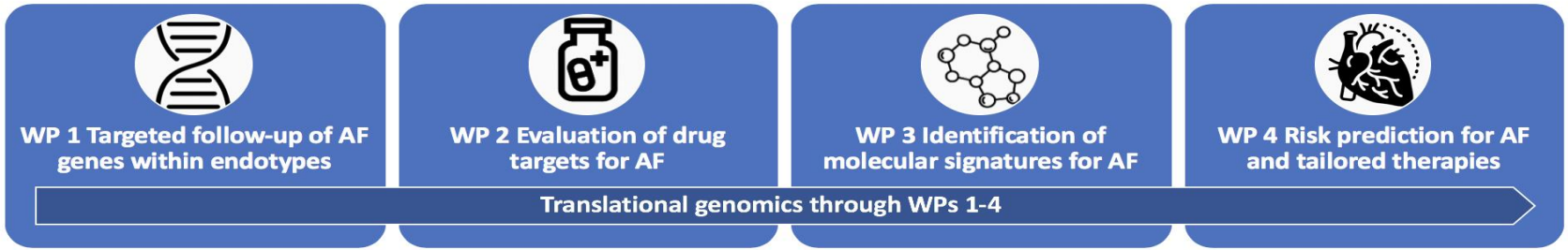
Nat Genet. 2014 Apr;46(4):357-63. doi: 10.1038/ng.2915. Epub 2014 Mar 2.

Loss-of-function mutations in SLC30A8 protect against type 2 diabetes.

Flannick J[1], Thorleifsson G[2], Beer NL[3], Jacobs SB[4], Grarup N[5], Burtt NP[4], Mahajan A[6], Fuchsberger C[7], Atzmon G[8], Benediktsson R[9], Blangero J[10], Bowden DW[11], Brandslund I[12], Brosnan J[13], Burslem F[14], Chambers J[15], Cho YS[16], Christensen C[17], Douglas DA[18], Duggirala R[19], Dymek Z[4], Farjoun Y[4], Fennell T[4], Fontanillas P[4], Forsén T[19], Gabriel S[4], Glaser B[20], Gudbjartsson DF[2], Hanis C[21], Hansen T[22], Hreidarsson AB[9], Hveem K[23], Ingelsson E[24], Isomaa B[25], Johansson S[26], Jørgensen T[27], Jørgensen ME[28], Kathiresan S[29], Kong A[2], Kooner J[30], Kravic J[31], Laakso M[32], Lee JY[33], Lind L[34], Lindgren CM[35], Linneberg A[36], Masson G[2], Meitinger T[37], Mohlke KL[38], Molven A[39], Morris AP[40], Potluri S[41], Rauramaa R[42], Ribel-Madsen R[5], Richard AM[13], Rolph T[13], Salomaa V[43], Segrè AV[44], Skärstrand H[18], Steinthorsdottir V[2], Stringham HM[7], Sulem P[2], Tai ES[45], Teo YY[46], Teslovich T[7], Thorsteinsdottir U[47], Trimmer JK[13], Tuomi T[48], Tuomilehto J[49], Vaziri-Sani F[18], Voight BF[50], Wilson JG[51], Boehnke M[7], McCarthy MI[52], Njølstad PR[53], Pedersen O[5]; Go-T2D Consortium; T2D-GENES Consortium, Groop L[54], Cox DR[41], Stefansson K[47], Altshuler D[55].

Atrial fibrillation

- 60 k cases and 930 k controls
- Identified 142 independent risk variants at 111 loci (80 novel), explaining 11.2% of the variation in atrial fibrillation.
- For functional follow-up,
  - integrated information on tissue and cell specific gene expression,
  - genomic regulatory elements and electrocardiogram (ECG) parameters from >62,976 Icelanders in sinus rhythm.
- Prioritized *MYH6* and *MYH7* as two of the most likely functional genes, supported by experiments in rabbits.



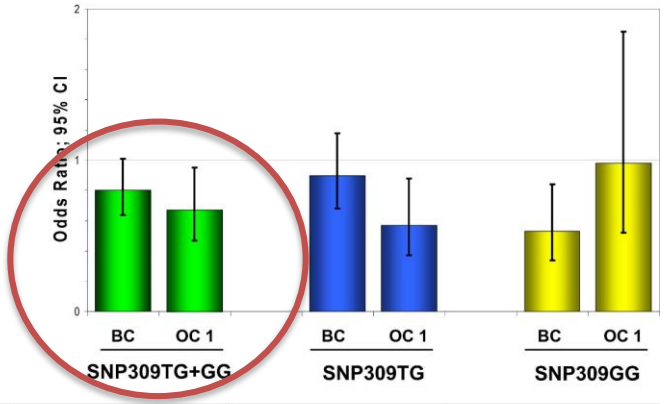
Nielsen JB et al. Biobank-driven genomic discovery yields new insight into atrial fibrillation biology, Nat Genet 2018

- To identify causal relations
  - *Budu-Aggrey A et al Evidence of a **causal relationship between body mass index and psoriasis:** A mendelian randomization study. PLoS Med 2019*
  - *Brumpton BM et al Variation in Serum PCSK9, Cardiovascular Disease Risk, and an Investigation of **Potential Unanticipated Effects of PCSK9 Inhibition**. Circ Genom Precis Med. 2019*

- Methodological development
  - *Brumpton B et al. Within-family studies for Mendelian randomization: avoiding dynastic, assortative mating, and population stratification biases. bioRxiv 602516; doi: https://doi.org/10.1101/602516*
  - *Zhou W et al. Efficiently controlling for **case-control imbalance and sample relatedness** in large-scale genetic association studies. Nat Genet 2018*

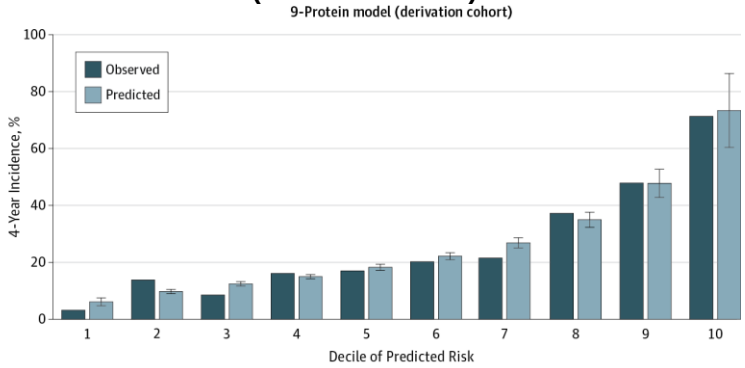
Knappskog S et al. The *MDM2* Promoter SNP285C/309G Haplotype Diminishes Sp1 Transcription Factor Binding and **Reduces Risk for Breast and Ovarian Cancer in Caucasians**
***Cancer Cell* 2011 19, 273-282**

- A MDM2 promoter polymorphism, SNP285G > C, is residing on the SNP309G allele.
- 7.7% (95% CI 7.6%–7.8%) of healthy individuals carry the SNP285C/309G haplotype.
- **Study population recruited from CONOR**
  - Ovarian cancer (n = 1993)
  - Breast cancer (n = 1973)
  - Healthy controls (n = 3646)
- SNP285C reduced the risk in both
  - ovarian cancer **(OR 0.74; CI 0.58–0.94)** and
  - breast cancer **(OR 0.79; CI 0.62–1.00)**



	HC	BC	OC 1	HC	BC	OC 1	HC	BC	OC 1
SNP285GG									
n	1232	1038	486	993	813	406	239	225	80
(%)	**(86.3)**	**(88.9)**	**(90.7)**	**(88.3)**	**(89.3)**	**(92.9)**	**(78.6)**	**(87.2)**	**(80.8)**
SNP285GC									
n	196	130	50	131	97	31	65	33	19
(%)	**(13.7)[1]**	**(11.1)[2]**	**(9.3)[3]**	**(11.7)**	**(10.7)**	**(7.1)**	**(21.4)[1]**	**(12.8)[2]**	**(19.2)[3]**
OR		0.79[4]	0.67		0.91[4]	0.57		0.55[4]	0.98
CI (95%)		0.62 1.00	0.47 0.95		0.69 1.20	0.37 0.88		0.35 0.86	0.52 1.85
P-value[5]		0.031	0.011		0.525	0.007		0.006	0.606

Predicting CVD-events on protein based biomarkers (Somascan)

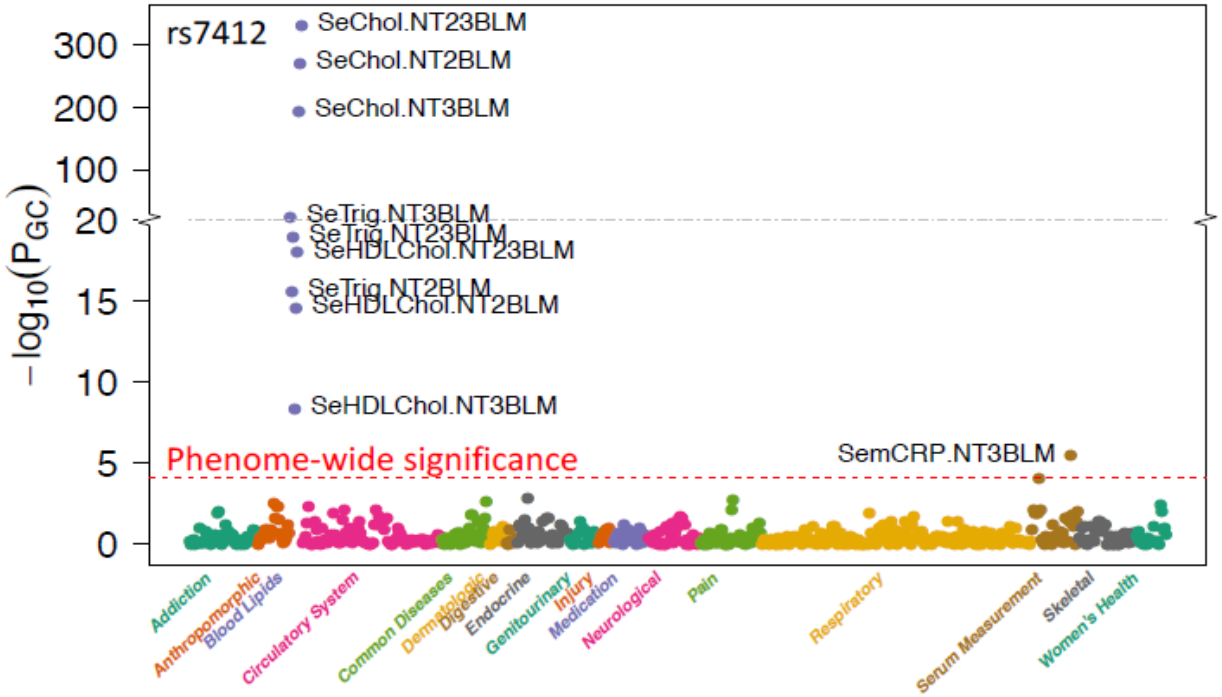


Median predicted risk, % (range)	6.2 (2.3 to <8.4)	9.7 (8.4 to <11.1)	12.4 (11.1 to <13.7)	15.0 (13.7 to <16.4)	18.2 (16.4 to <20.2)	22.2 (20.2 to <24.1)	26.7 (24.1 to <30.5)	34.8 (30.5 to <39.9)	48.3 (39.9 to <56.8)	69.1 (56.8 to 99.9)
No. of events	3	13	8	15	16	19	20	35	45	67
No. of participants	94	94	94	93	94	94	93	94	94	94

Agreement Between Observed vs Predicted 4-Year Incidence of Myocardial Infarction, Stroke, Heart Failure, and Death With the 9-Protein Model

Ganz P, Heidecker B, Hveem K, Jonasson C, Kato S, Segal MR, Sterling DG, Williams SA.
Development and Validation of a Protein-Based Risk Score for Cardiovascular Outcomes Among Patients With Stable Coronary Heart Disease
JAMA. 2016;315(23):2532-2541.

PheWas analyses are presented on HUNT pheweb based on summary statistics from multiple GWAS



APOE:p.Arg176 Cys (rs7412) associated with

- Alzheimers disease,
- fasting blood lipids and
- dyslipidemia

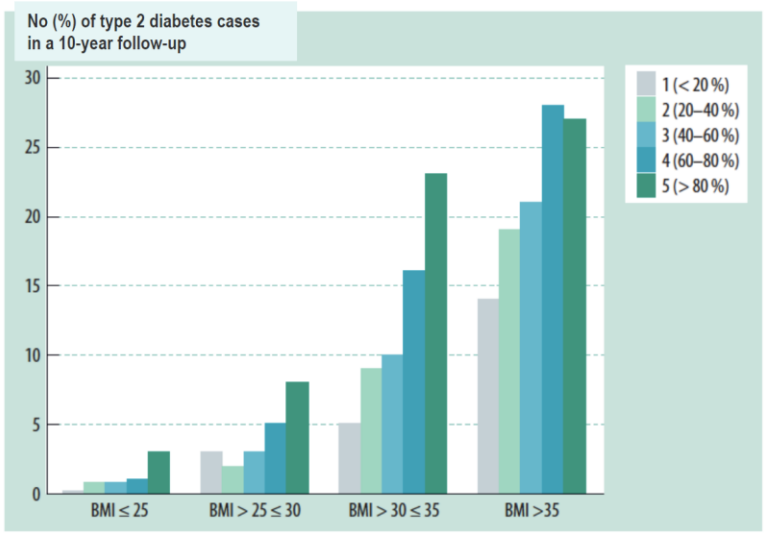
Pre-competitive collaborations to promote large-scale analyses (population based)

- **Sequencing**
  - WES of 15 000 -100 000 in the planning face
- **Metabolomics**
  - 20 000 within next 12 months (*Nightingale)*
  - 78 000 (26 000x3 – H2,H3,H4) – in the planning face (*Metabolon*)
- **Proteomics**
  - Somascan – aptamer-based assay optimized for protein biomarker discovery, 3000 CVD-related subjects based on a both protein based arrays (1500/5000 proteins pr array) *(SomaLogic)*
  - Microbiota -14 000 fully characterized within 6 months *(Bio-Me)*
- **Other biomarkers**
  - Troponin I – 10 000 HUNT2, 6000 HUNT3, 35 000 HUNT4 *(Abbot)*

Polygenic Risk Scores (FinnGen)

COMPARISON OF PRS AND BMI IN TYPE 2 DIABETES

Genetic risk brings added personalized value to the disease prevention regardless of lifestyle

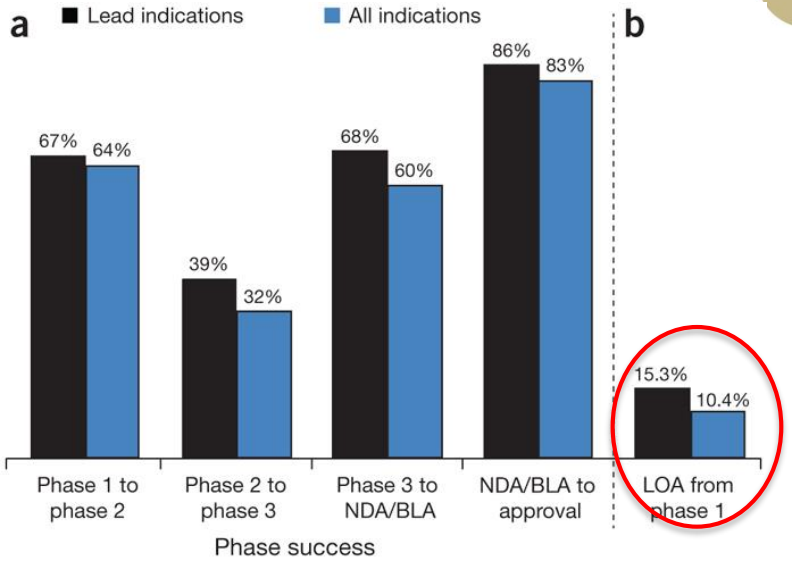


Perola et al Duodecim 2019

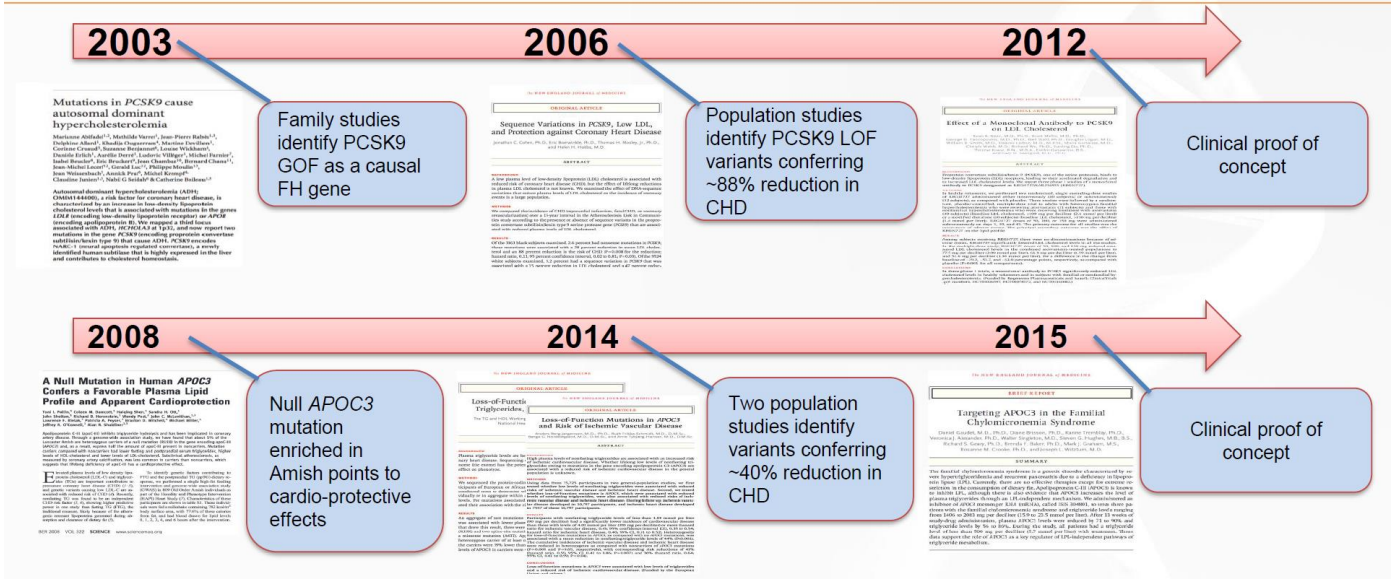
Biobank driven drug discoveries

Development of therapeutics in 2018

- Only **1 of 10** drug candidates reach the market
- Most failures occur in Phase II clinical trials
  - **50%** due to lack of efficacy
  - **25%** due to toxicity
- Pre-clinical models may be poor predictors of clinical benefit
- Compounds supported by human genetics evidence **are 2,5x more likely to succeed**
- The total costs of one successful drug is ~ $2,8 billion



The Potential for Human Genetics to Accelerate Target Identification, Validation and Drug Development



Alan Shuldiner, 2018

Stein EA, et al Effect of a monoclonal antibody to PCSK9, REGN727/SAR236553, to reduce low-density lipoprotein cholesterol in patients with heterozygous familial hypercholesterolaemia on stable statin dose with or without ezetimibe therapy: a phase 2 randomised controlled trial. Lancet. 2012

Potential drug targets based on HUNT-related genetic discoveries

***MEPE*-gene**,

associated with reduced bone mineral density and risk of fracture

- *Ida Surraka et al. Loss-of-function mutation in the MEPE gene is associated decreased bone mineral density and increased risk for fractures and osteoporosis–submitted*
- *Cristopher V et al . Whole exome sequencing and characterization of coding variation in 49,960 individuals in the UK Biobank. bioRxiv 572347; doi: https://doi.org/10.1101/572347*

ZNF529-gene,

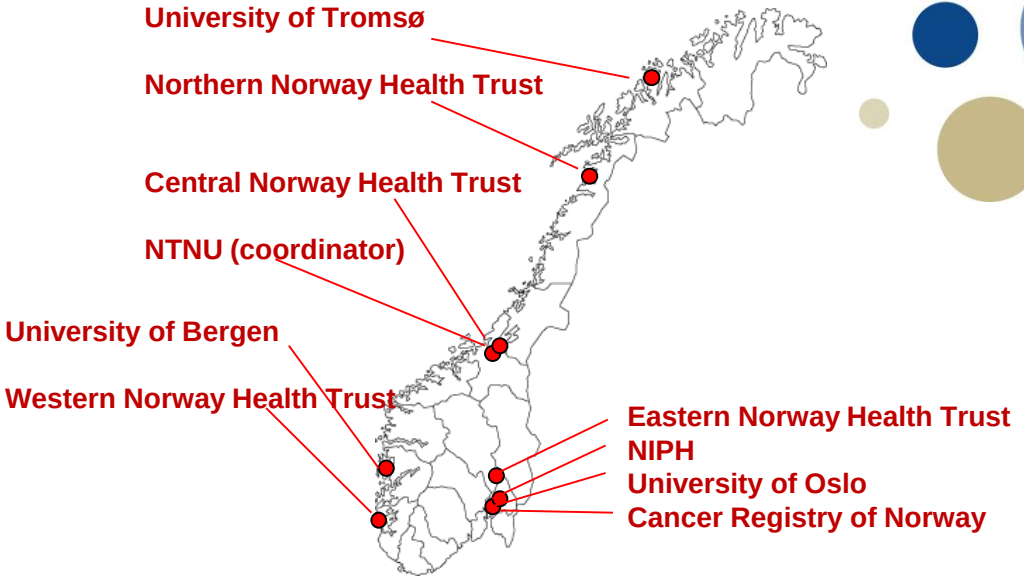
A novel LoF variant, *ZNF529*:p.K405X, associated with decreased levels of LDL-C ($P=1.3\times10^{-8}$) but demonstrated no association with liver enzymes or non-fasting blood glucose levels.

Silencing of *ZNF529* in human hepatocytes resulted in upregulation of LDL receptor (LDLR) and increased LDL-C uptake in the cells, suggesting that inhibition of *ZNF529* or its gene product could be used for treating hypercholesterolemia and hence reduce the risk of CVD.

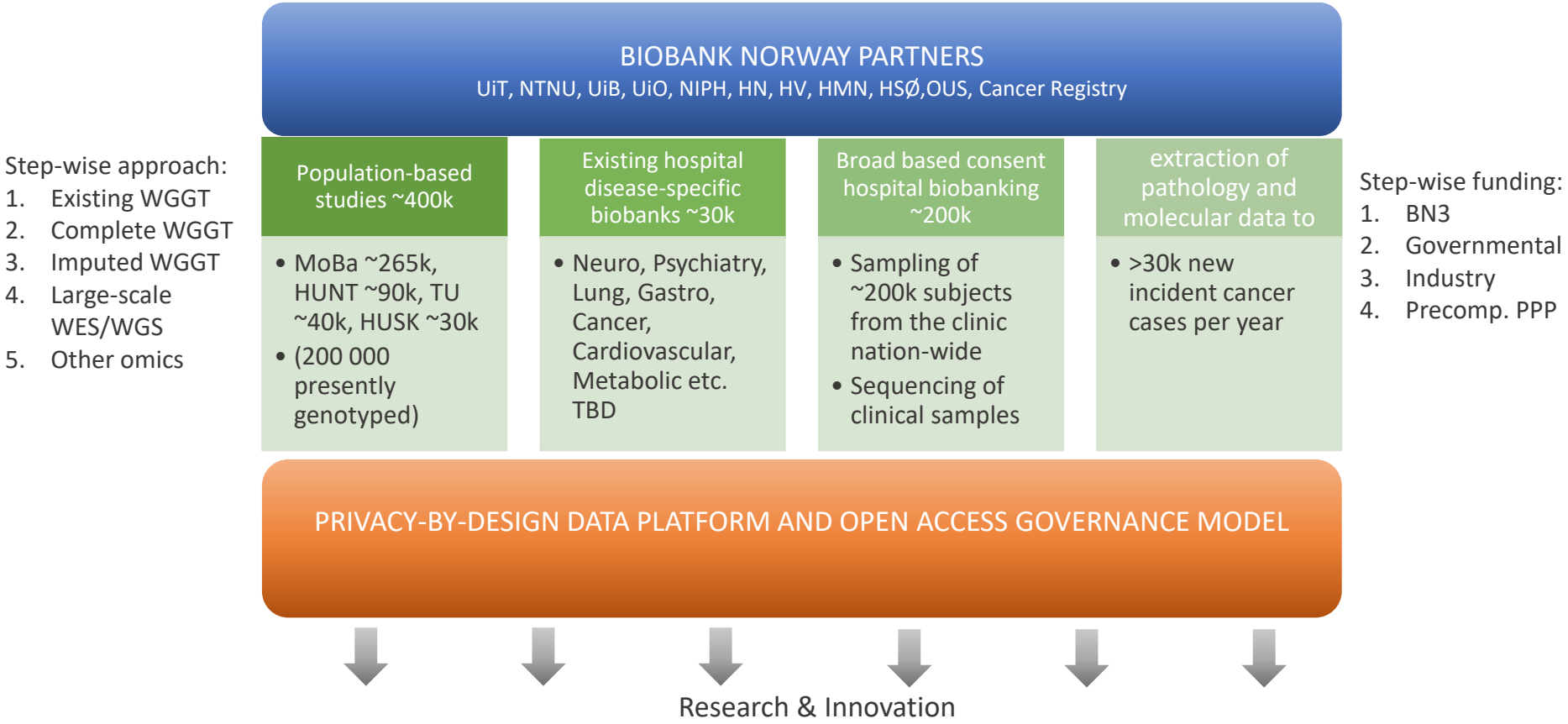
- *Jonas B. Nielsen et al. Loss-of-function genomic variants with impact on liver-related blood traits highlight potential therapeutic targets for cardiovascular disease. bioRxiv 597377, doi: https://doi.org/10.1101/597377*

Biobank Norway

A National Biobank Infrastructure since 2010



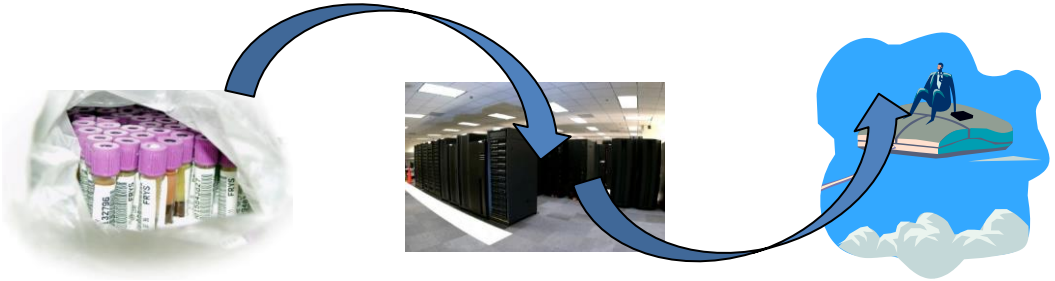
- Observer state of BBMRI-ERIC since 2013
- Full member state of BBMRI-ERIC since 2016
- Funded with 215 mill NOK by the Research Council of Norway



WGGT=whole genome genotyping, WES=Whole exome sequencing, WGS=Whole genome sequencing,

Data storage, access and analyses

Digitizing biobanks – the future perspectives



A shift from samples to data (digitalization)

- Reduced costs for access to larger sample sizes (omics-driven analyses) as a trade off for significant return of results to the biobank
- Increased costs for data storage
- Increased focus on data security (GDPR)
- Reduction of data export, researchers will be granted virtual access to data clouds e.g. HUNT Cloud, TSD, SAFE, HAP….. , also offering computational capacity
- Biobanks will play a stronger role in precision medicine
- Access to annotated biobank samples and national registry data will be centralized to publicly governed Health data platforms and Health analyses platforms

Ethical considerations and return of results

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Ethics, openness and dissemination

- Attendance rate and public support is highly dependant on trust
- All projects are approved by both the REC and HUNT-Data Access Committee
- Transparency is encouraged by active use of webpages (e.g. www.hunt.no) with updates on on-going research projects, project resumé, recent and previous publications and new findings.
- Communcation with the donor community is encouraged and a “my page” for research participants on www.helsenorge.no is established for all HUNT4-participants.

- Do you want feedback of results if the genetic information obtained may result in potential treatment or preventive measures
  - **93 % yes**
- Are you willing to participate in follow-up studies based on genetic findings with no clear clinical impact
  - **84 % yes**

Return of results

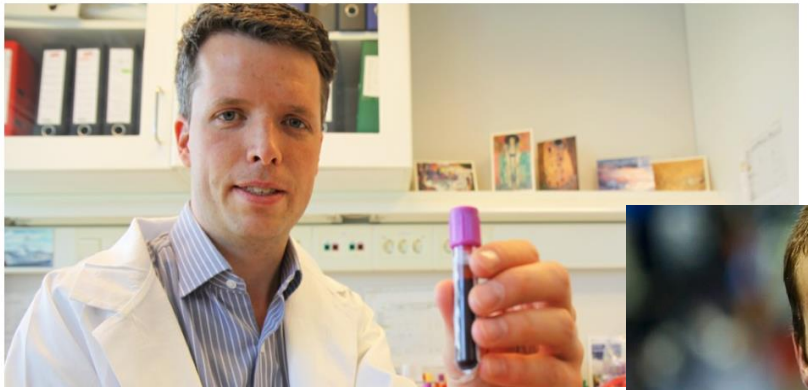
- International recommendations:
  Genetic information/risk must be "actionable" to trigger a feedback.
  - Provided good opportunities for prevention, or even treatment, the situation most commonly is referred to as actionable
  - The researchers must then plan for feedback (Biotechnology act

- Based on WES 3,5 % have actionable results (Geisinger)

- Other markers? Genetic risk scores?

Familiar Hypercholesterolemia (FH)

- 25.000 Norwegians have the same disease as Dale Oen
  - Many of us are carriers of a serious condition such as FH without knowing



Alexander Fredriksen
Journalist

Publisert 10.06.2015, kl. 22:22

21 women had their breasts and ovaries removed – should never been operated

21 kvinner som fikk operert bort brystene, eggstokkene eller begge deler, ved OUS mellom 2002 og 2014, har fått beskjed om at de egentlig ikke skulle blitt operert.

Patients were all wrongly advised about their BRCA-mutation related breast cancer risk. A 12 - 34 year follow-up of ~40 000 women in HUNT will have the potential to describe the population risk more precisely

Summary and conclusions

- Population studies offer a unique prospective longitudinal design for biomarker discovery and validation
- Large scale omics analyses in combination with health data, physical examination and access to a large number of phenotypes also creates a comprehensive research platform for biomarker discovery
- The future of drug discovery and precision medicine is presently fueled by biobank based human genomic discovery
- Genetic “experiments of nature” can inform therapeutic target discovery and provide insight into new mechanism (LoF)
- “Biological recall” is accepted
- Return of medically genetic actionable results will affect health care resources to realize downstream health and economic benefits
- Partnership between industry, academia and health care systems can accelerate genomic discovery and implementation of precision medicine

Key personnel,

NTNU
K.G. Jebsen Center for Genetic Epidemiology

STIFTELSEN KRISTIAN GERHARD JEBSEN

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- **Maiken Elvestad Gabrielsen,** Center Coordinator
- **Pål Sætrom,** Professor Bioinformatics,
- **Bjørn Olav Åsvold,** Professor, Epidemiology MR/
- **Eivind Almås,** Professor Systems Biology
- **Oddgeir Lingaas Holmen**, MD, PhD, PI/Head of HUNT Data Center/HUNT Cloud,
- **Anne Heidi Skogholt**, Coordinator, Analyses group
- **Ben Brumpton,** Senior Researcher, MR/GWAS
- **Mari Løset,–** Post doc/Expression analysis
- **Humaira Rasheed,** Post doc, MR
- **Eirin Haug,** PhD, Post doc
- **Ailin Falkmo Hansen**, PhD, Post doc
- **Gunnhild Aaberg Vie**, PhD, Post doc
- **Christian Jonasson,** Researcher pharmacogenomics
- **Laurent Thomas** – Bioinformatics, Applied biostatistics
- **Eivind Coward**, Bioinformatics
- **Endre Bakken Stovner**, System developer, PhD-student
- **Tom Erik Røberg** – Data administrator, HUNT Cloud
- **Sandor Zeestraten** – Data administrator, HUNT Cloud
- **Qussay Ghazeia**, Quality management, HUNT Cloud
- **Matus Kosut,** Programmer, HUNT Cloud
- **Siv Hege Stemshaug,** MD, PhD student
- **Ole Jørgen Bekkevold** MD, PhD student
- **Marta Riise Moksnes**, PhD-student
- **Kjartan Øvretveit**, PhD-student
- **Lars Ursin, PhD,** Assoc prof., ethicist
- **Jonas Bille Nielsen**, MD, PhD, Researcher,
- **Maria Brandkvist,** PhD-student
- **Janne Tellefsen**, Communication
- **Åshild Solvin**, medical student/Student Research Program
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Thank you

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