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GENETICS AND GENOMICS
QGG

# Use of Whole Genome Sequence variants in genomic prediction

# GenSAP challenges

- Use of full sequence data
  - Inc integration of external information
- Predictions across breeds and populations
- Plants and new animal species
- Non-additive genetic effects
- Analysis of large datasets
- Estimation and control of inbreeding using Genomics

# Lessons learned

- Sequence include causal and high LD variants
- Real data: More markers only marginally improve predictions
  - Real data: HD ≈ 54K (Su et al., 2012)
  - Imputed WGS ≈ HD (Van Binsbergen et al., 2015 )
- Theoretic study by Van den Berg et al., 2016 (SFA2)
  - Small improvements within breeds
  - Across breeds: Only use markers very close to causal variants (others add noise)
- Low MAF variants are poorly imputated

# Lessons learned

- Not all SNPs are equal
- Feature models may improve predictions (SFA1)
  - Need SNP set highly enriched with causal and high LD variants
  - Best in for unrelated individuals
- Bayesian Variable Selection Models (SFA2)
  - Discriminate between high/low variance SNPs
  - Require high computation time
- Weighted G(SNP)BLUP can specify identical models/predictions (Su et al., 2014) (SFA2)

# Challenge

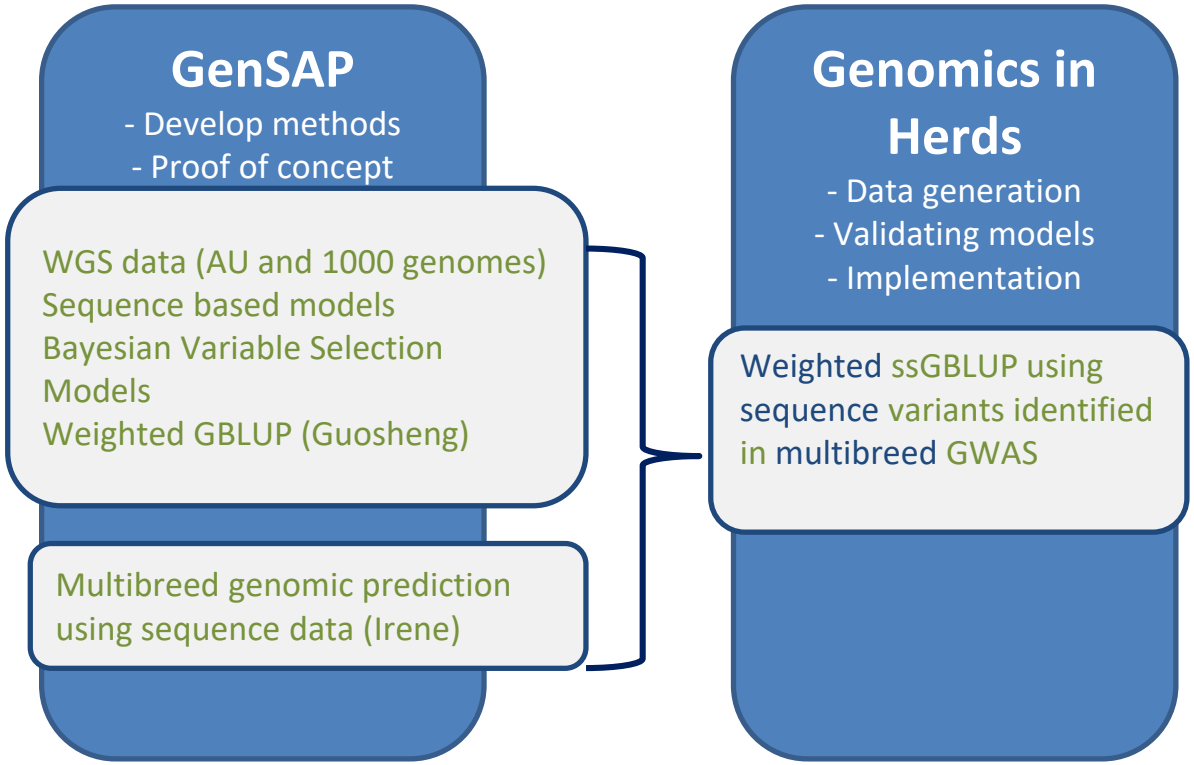
**Can we develop models that:**

- **improve genomic predictions by using whole genome sequence variants**
- **Can be implemented in routine evaluations**

# Strategy to meet challenge

- Identify set of SNPs enriched with causal variants
  1. GWAS using multi breed data: Identify 3-5 top SNPs/QTL
  2. Functional annotated information
- Genotype large number of cows (custum chip)
- Estimate parameters in BVS models or genomic feature model
- Develop equivalent model by weighted G(SNP)BLUP

# GenSAP and industry projects



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# Using additional SNPs selected from whole genome sequence (WGS) data for genomic prediction in Danish Jersey

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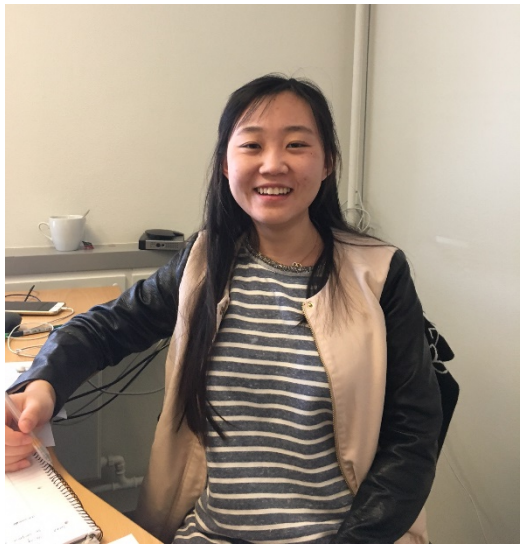
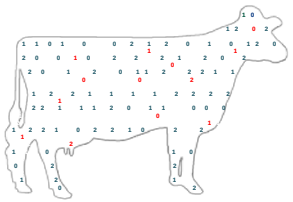
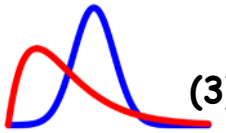
INRA SCIENCE & IMPACT



# Objectives



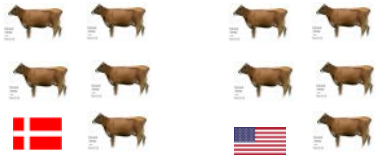
(1) 54 K +
SNPs selected from WGS



(3) Models



(2) Joint reference

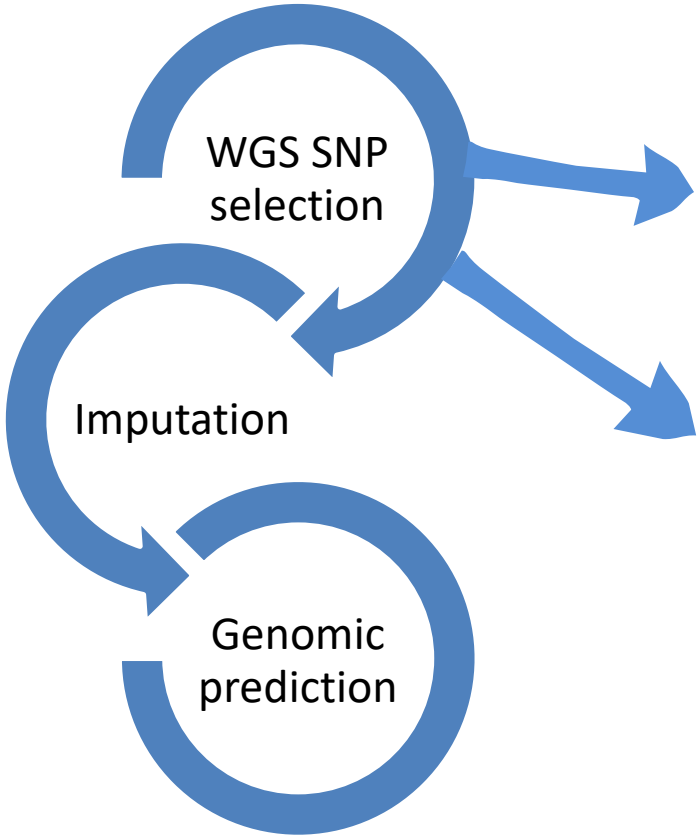


Reliable
genomic prediction

- Investigate effects of additional WGS SNPs on genomic prediction
- Effects of using additional WGS SNPS in a joint reference
- Assessed models on their efficiency to use information of additional WGS SNPs

# Workflow






**NOR SNPs (Goutam, Bernt, Xiaoping, Zexi)**

- peaks of QTL from Nordic Holsteins, Nordic Red and Danish Jersey

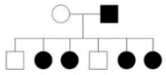
**FR SNPs (Didier et al.)**

- literature
- a strong variant effect predictor annotation (e.g. non-synonymous substitution)
- regulatory regions of genes
- peaks of QTL
- breakpoints of structural variants

# Imputation

**Animal**
- DK bulls: ~1,300
- US bulls: ~1,200
- DK cows: ~31,000

**Genotype**
- 54K chip
- standard LD chip
- customized LD chip
  - standard LD chip
  - NOR SNPs
  - FRA SNP



**Pedigree**
- 6,100 males
- 66,000 females

**Two-step imputation**
*(Fimpute)*

(1)

**54K**

(2)

**54K**
**+ NOR SNPs + FRA SNPs**

# Reference and validation populations

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- **Validation**
  - genotyped cows born after 2014-01-01
  - these cows and their paternal female half-sibs born after 2008-07-01 as cow validation set
  - excluding the half-sib families with size > 500
  - **5,829 validation cows from 155 paternal half-sib families**

- **Reference**
  - validation cows' maternal female and male half-sibs born after 2008-07-01 were excluded
  - progenies of these animals (validation cows and the sibs) were removed

| Reference | N_BULL | N_COW |
|---|---|---|
| COW | -- | 8,763 |
| DK | 1,282 | -- |
| DKUS | 2,430 | -- |
| DKCOW | 1,282 | 8,602 |
| DKUSCOW | 2,430 | 8,602 |

# Prediction: GBLUP and BVS models

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- **One-component model**

$$y = 1\mu + X\,g + e$$

54K/ 54K+selected WGS SNPs

| Scenarios |
|---|
| 54K |
| 54K_NOR |
| 54K_FRA |
| 54K_NOR_FRA |

- **Two-component model**

$$y = 1\mu + X_{54K}g_{54K} + X_{WGS}g_{WGS} + e$$

54K — Selected WGS SNPs

| Component_One | Component_Two |
|---|---|
| 54K | NOR |
| 54K | FRA |
| 54K | NOR+FRA |

Bootstrap to asses significance

# Prediction: validation on cows

**Milk**

**GBLUP**

| Reference | PBLUP | 54K G1 |
|---|---|---|
| DK[1] | 13.2 | 31.2 |
| DKUS[2] | 17.4 | 41.5 |
| COW[3] | 10.5 | 56.3 |
| DKCOW[4] | 14.9 | 59.8 |
| DKUSCOW[5] | 18.9 | 63.7 |

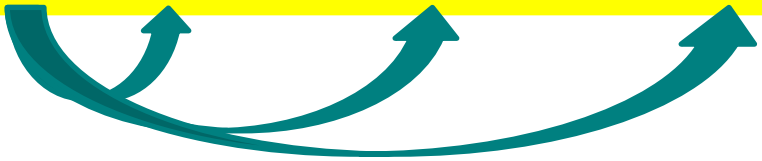
Large improvement with increased reference

# GBLUP: Large improvements from sequence variants

**Milk**

**GBLUP**

| Reference | PBLUP | 54K | 54K + NOR | | 54K + FRA | | 54K+ NOR + FRA | |
|---|---|---|---|---|---|---|---|---|
| | | G1 | G1 | G2 | G1 | G2 | G1 | G2 |
| DK[1] | 13.2 | 31.2 | 40.0 | | 40.7 | | 42.8 | |
| DKUS[2] | 17.4 | 41.5 | 51.7 | | 52.2 | | 53.6 | |
| COW[3] | 10.5 | 56.3 | 64.1 | | 65.0 | | 65.3 | |
| DKCOW[4] | 14.9 | 59.8 | 67.8 | | 68.4 | | 69.0 | |
| DKUSCOW[5] | 18.9 | 63.7 | 70.4 | | 71.0 | | 71.4 | |



Large improvement by adding sequence variants

# Models

**Milk**

**GBLUP**

| Reference | PBLUP | 54K | 54K + NOR | | 54K + FRA | | 54K+ NOR + FRA | |
|---|---|---|---|---|---|---|---|---|
| | | G1 | G1 | G2 | G1 | G2 | G1 | G2 |
| DK[1] | 13.2 | 31.2 | 40.0 | 45.3 | 40.7 | 45.5 | 42.8 | 46.0 |
| DKUS[2] | 17.4 | 41.5 | 51.7 | 54.4 | 52.2 | 54.5 | 53.6 | 55.1 |
| COW[3] | 10.5 | 56.3 | 64.1 | 64.5 | 65.0 | 65.9 | 65.3 | 65.4 |
| DKCOW[4] | 14.9 | 59.8 | 67.8 | 69.5 | 68.4 | 69.7 | 69.0 | 70.0 |
| DKUSCOW[5] | 18.9 | 63.7 | 70.4 | 71.6 | 71.0 | 71.8 | 71.4 | 72.0 |

**BVS**

| Reference | PBLUP | 54K | 54K + NOR | | 54K + FRA | | 54K+ NOR + FRA | |
|---|---|---|---|---|---|---|---|---|
| | | B1 | B1 | B2 | B1 | B2 | B1 | B2 |
| DK[1] | 13.2 | 41.3 | 47.5 | 48.2 | 48.2 | 49.9 | 48.6 | 48.3 |
| DKUS[2] | 17.4 | 50.6 | 57.3 | 57.4 | 57.2 | 57.8 | 57.8 | 58.1 |
| COW[3] | 10.5 | 64.4 | 67.3 | 67.0 | 67.5 | 62.4 | 67.5 | 67.7 |
| DKCOW[4] | 14.9 | 71.2 | 71.6 | 71.6 | 48.3 | 72.2 | 72.0 | 72.2 |
| DKUSCOW[5] | 18.9 | 71.2 | 73.8 | 73.7 | 74.0 | 73.9 | 74.0 | 74.2 |

Bayesian models better than GBLUP

# Improvement from WGS SNPs and models for milk yield

## Milk

**GBLUP**

| Reference | PBLUP | 54K | 54K + NOR | | 54K + FRA | | 54K+ NOR + FRA | |
|---|---|---|---|---|---|---|---|---|
| | | G1 | G1 | G2 | G1 | G2 | G1 | G2 |
| DK[1] | 13.2 | 31.2 | 40.0 | 45.3 | 40.7 | 45.5 | 42.8 | 46.0 |
| DKUS[2] | 17.4 | 41.5 | 51.7 | 54.4 | 52.2 | 54.5 | 53.6 | 55.1 |
| COW[3] | 10.5 | 56.3 | 64.1 | 64.5 | 65.0 | 65.9 | 65.3 | 65.4 |
| DKCOW[4] | 14.9 | 59.8 | 67.8 | 69.5 | 68.4 | 69.7 | 69.0 | 70.0 |
| DKUSCOW[5] | 18.9 | 63.7 | 70.4 | 71.6 | 71.0 | 71.8 | 71.4 | 72.0 |

**BVS**

| Reference | PBLUP | 54K | 54K + NOR | | 54K + FRA | | 54K+ NOR + FRA | |
|---|---|---|---|---|---|---|---|---|
| | | B1 | B1 | B2 | B1 | B2 | B1 | B2 |
| DK[1] | 13.2 | 41.3 | 47.5 | 48.2 | 48.2 | 49.9 | 48.6 | 48.3 |
| DKUS[2] | 17.4 | 50.6 | 57.3 | 57.4 | 57.2 | 57.8 | 57.8 | 58.1 |
| COW[3] | 10.5 | 64.4 | 67.3 | 67.0 | 67.5 | 62.4 | 67.5 | 67.7 |
| DKCOW[4] | 14.9 | 68.5 | 71.6 | 71.6 | 48.3 | 72.2 | 72.0 | 72.3 |
| DKUSCOW[5] | 18.9 | 71.2 | 73.8 | 73.7 | 74.0 | 73.9 | 74.0 | 74.2 |

1)54K+ WGS > 54K
2) Reference increase, 54K+ WGS > 54K

3) Bayesian > GBLUP
2) Two > one for GBLUP, not consist for Bayesian

Potential: 63.7 → 74.2

# Improvement from WGS SNPs and models for protein yield

## Protein

**GBLUP**

| Reference | PBLUP | 54K | 54K + NOR | | 54K + FRA | | 54K+ NOR + FRA | |
|---|---|---|---|---|---|---|---|---|
| | | G1 | G1 | G2 | G1 | G2 | G1 | G2 |
| DK[1] | 17.5 | 26.6 | 29.2 | 30.4 | 29.9 | 30.7 | 30.7 | 31.0 |
| DKUS[2] | 20.9 | 32.7 | 35.7 | 36.7 | 36.3 | 36.8 | 37.0 | 37.2 |
| COW[3] | 11.6 | 35.8 | 38.6 | 38.2 | 39.6 | 39.7 | 39.7 | 39.3 |
| DKCOW[4] | 15.0 | 39.0 | 42.1 | 42.7 | 42.8 | 43.2 | 43.1 | 43.3 |
| DKUSCOW[5] | 17.8 | 41.9 | 44.5 | 44.7 | 45.0 | 45.2 | 45.2 | 45.2 |

**BVS**

| Reference | PBLUP | 54K | 54K + NOR | | 54K + FRA | | 54K+ NOR + FRA | |
|---|---|---|---|---|---|---|---|---|
| | | B1 | B1 | B2 | B1 | B2 | B1 | B2 |
| DK[1] | 17.5 | 29.1 | 30.9 | 31.0 | 31.4 | 31.1 | 31.5 | 30.7 |
| DKUS[2] | 20.9 | 36.2 | 38.4 | 38.2 | 38.2 | 37.6 | 38.5 | 37.6 |
| COW[3] | 11.6 | 38.1 | 39.6 | 39.4 | 40.2 | 40.4 | 40.1 | 39.8 |
| DKCOW[4] | 15.0 | 41.7 | 43.6 | 43.6 | 31.1 | 44.2 | -- | -- |
| DKUSCOW[5] | 17.8 | 44.7 | 46.0 | 46.0 | 46.1 | 46.2 | -- | -- |

Same conclusions but at lower level

Potential: 41.9 → 46.2

# Improvement from WGS SNPs and models for fat yield

## Fat

**GBLUP**

| Reference | PBLUP | 54K | 54K + NOR | | 54K + FRA | | 54K+ NOR + FRA | |
|---|---|---|---|---|---|---|---|---|
| | | G1 | G1 | G2 | G1 | G2 | G1 | G2 |
| DK[1] | 19.9 | 26.7 | 28.1 | 28.3 | 27.7 | 27.4 | 28.2 | 27.8 |
| DKUS[2] | 21.4 | 29.8 | 31.3 | 31.3 | 30.9 | 30.7 | 31.3 | 31.1 |
| COW[3] | 14.8 | 33.1 | 33.9 | 34.0 | 34.1 | 34.3 | 34.3 | 34.5 |
| DKCOW[4] | 22.2 | 37.1 | 37.7 | 37.6 | 37.6 | 37.7 | 37.8 | 37.8 |
| DKUSCOW[5] | 23.1 | 37.9 | 38.6 | 38.6 | 38.4 | 38.4 | 38.6 | 38.6 |

**BVS**

| Reference | PBLUP | 54K | 54K + NOR | | 54K + FRA | | 54K+ NOR + FRA | |
|---|---|---|---|---|---|---|---|---|
| | | B1 | B1 | B2 | B1 | B2 | B1 | B2 |
| DK[1] | 19.9 | 27.2 | 28.2 | 28.5 | 27.8 | 27.6 | 28.3 | 27.6 |
| DKUS[2] | 21.4 | 30.4 | 31.6 | 31.6 | 31.0 | 30.5 | 31.5 | 30.9 |
| COW[3] | 14.8 | 33.7 | 34.2 | 26.8 | 34.5 | 34.5 | 34.6 | 34.7 |
| DKCOW[4] | 22.2 | 27.2 | 37.7 | 37.8 | 28.0 | 37.6 | 37.8 | 37.7 |
| DKUSCOW[5] | 23.1 | 39.0 | 39.1 | 39.2 | 38.9 | 38.7 | 38.9 | 38.9 |

Same tendencies but at lower level and not significant

Potential: 37.9 → 38.9

# Improvement from WGS SNPs and models for mastitis

## Mastitis

**GBLUP**

| Reference | PBLUP | 54K | 54K + NOR | | 54K + FRA | | 54K+ NOR + FRA | |
|---|---|---|---|---|---|---|---|---|
| | | G1 | G1 | G2 | G1 | G2 | G1 | G2 |
| DK[1] | 20.5 | 32.4 | 32.8 | 33.0 | 33.4 | 32.3 | 33.1 | 33.7 |
| DKUS[2] | 19.6 | 33.9 | 34.1 | 34.5 | 34.8 | 33.4 | 34.6 | 35.0 |
| COW[3] | 16.8 | 34.0 | 34.5 | 34.4 | 34.8 | -- | -- | 34.3 |
| DKCOW[4] | 15.4 | 39.8 | 40.2 | 40.6 | 40.9 | 40.4 | 40.4 | 40.9 |
| DKUSCOW[5] | 14.6 | 40.0 | 40.3 | 40.8 | 41.0 | 40.3 | 40.6 | 41.0 |

**BVS**

| Reference | PBLUP | 54K | 54K + NOR | | 54K + FRA | | 54K+ NOR + FRA | |
|---|---|---|---|---|---|---|---|---|
| | | B1 | B1 | B2 | B1 | B2 | B1 | B2 |
| DK[1] | 20.5 | 31.6 | 30.8 | 30.1 | 32.2 | 32.3 | 32.2 | 31.2 |
| DKUS[2] | 19.6 | 33.8 | 33.8 | 32.0 | 34.3 | 33.9 | 33.9 | 32.8 |
| COW[3] | 16.8 | 34.2 | 34.4 | 34.8 | 34.4 | 34.6 | 34.7 | 34.8 |
| DKCOW[4] | 15.4 | 39.3 | 39.4 | 39.4 | 40.4 | 40.4 | 40.3 | 40.3 |
| DKUSCOW[5] | 14.6 | 39.9 | 40.2 | 40.1 | 40.7 | 40.6 | 41.1 | 41.0 |

1) Minor improvements and not significant

## Conclusions

- **Using additional WGS SNPs improve reliabilities for production traits considerably (also wth larger reference)**
- **Bayesian VSM were better than GBLUP**
- **No clear differences between one-component and two-component models**
- **Improvements will be testet and implemented by Weighted-SS-SNPBLUP**
- **Further improvements**
  - Better understanding of genome → improvements for other traits
  - More sequence data → improved imputation → Better markers for LDchip

# CHALLANGE

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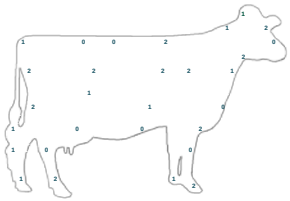
- Large scale ssG(SNP)BLUP
- Sequence information
- Bayesian methods
- Multitrait heterogeneous (co)variance models

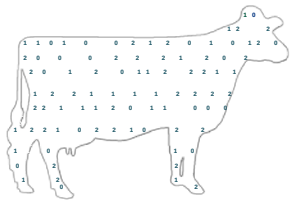
Integrate in model for rutine evaluation

# Background

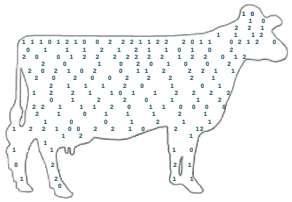
High throughput genotyping



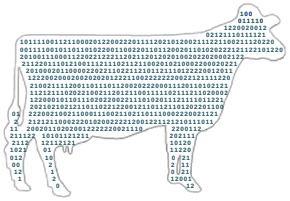
LD (7 K)



MD (54 K)



HD (777 K)



WGS (~26,700 K)

**Hypothesis**: Higher SNP density -> better LD -> higher reliability

**Real data:** HD ≈ 54K (Su et al., 2012) & Imputed WGS ≈ HD (Van Binsbergen et al., 2015 )

- Only causative mutations or variants very close to causative mutations can improve reliability

  (van den Berg et al., 2016)

- non-causative mutations bring noise

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# Current Danish (QGG) 'genomics in herds' team

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Goutam, Bernt, Guosheng, Mogens