GENETIC COUNSELING IN HORSE

M. Dequenne, J. Detilleux

Veterinary management of animal resources

University of Liège - Belgium

FARAH

LIÈGE université
Médecine Vétérinaire

WHAT DO THESE HORSES HAVE IN COMMON?

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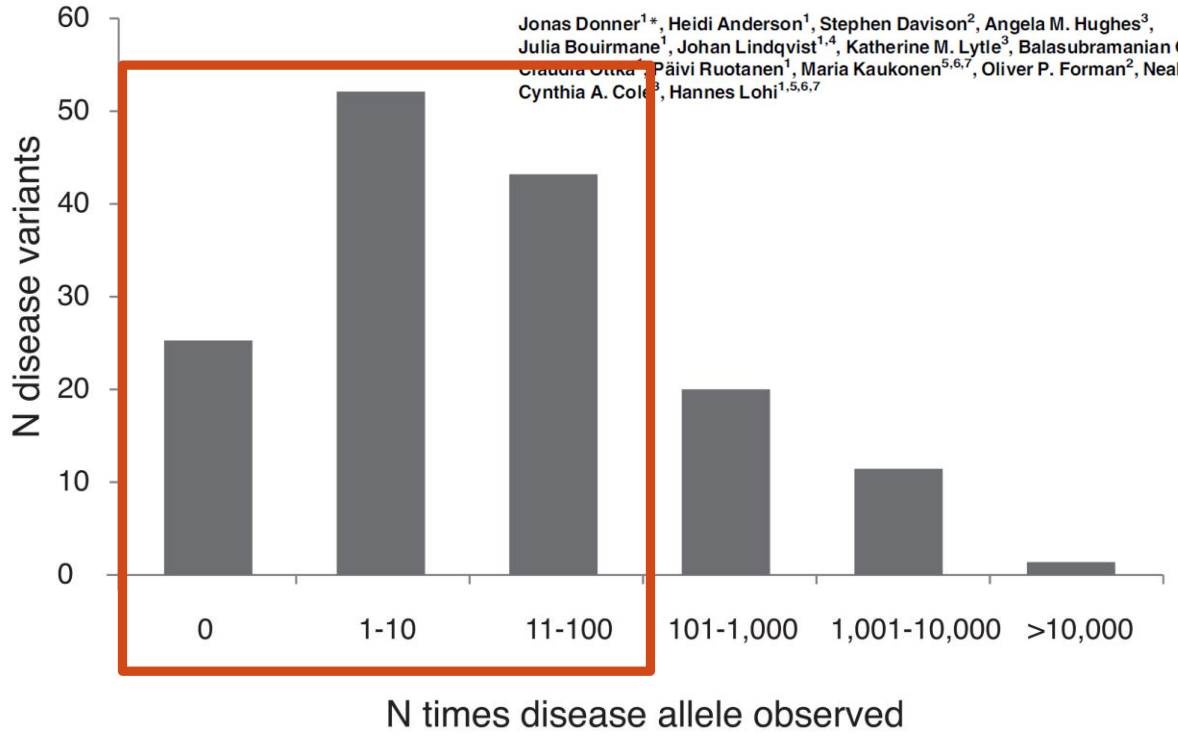
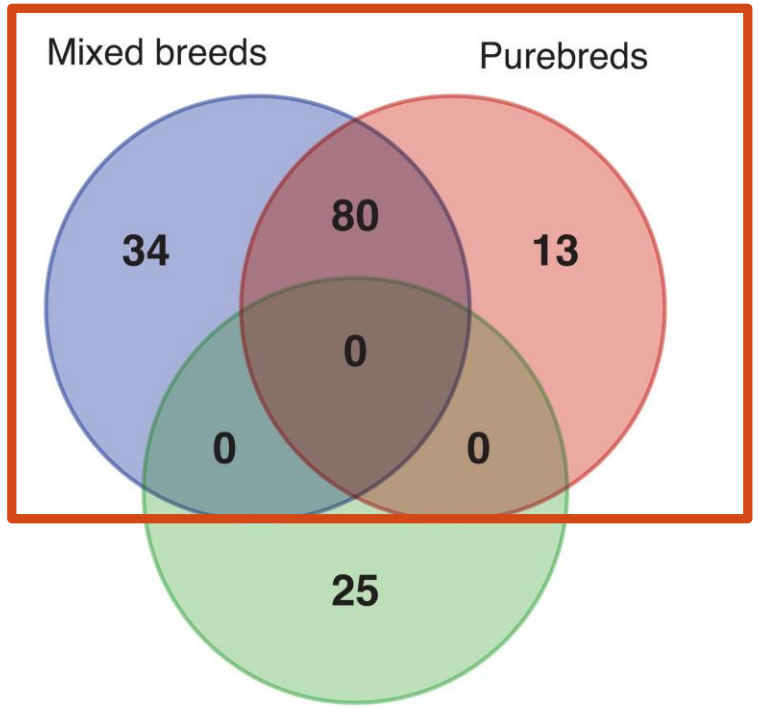
HIGH PREVALENCE OF BREED RELATED GENETIC DISEASES

Frequency and distribution of 152 genetic disease variants in over 100,000 mixed breed and purebred dogs

Jonas Donner[1]*, Heidi Anderson[1], Stephen Davison[2], Angela M. Hughes[3], Julia Bouirmane[1], Johan Lindqvist[1,4], Katherine M. Lytle[3], Balasubramanian Ganesan[3], Claudia Ottka[1], Päivi Ruotanen[1], Maria Kaukonen[5,6,7], Oliver P. Forman[2], Neale Fretwell[3], Cynthia A. Cole[3], Hannes Lohi[1,5,6,7]





HIGH PREVALENCE OF BREED RELATED GENETIC DISEASES

A review of scientific literature on inherited disorders in domestic horse breeds

CD Bettley[†], JM Cardwell[‡], LM Collins[§] and L Asher[#]*

49 breeds predisposed to >1 inherited disorders

Frequency of genetic diseases in AQHA subgroups

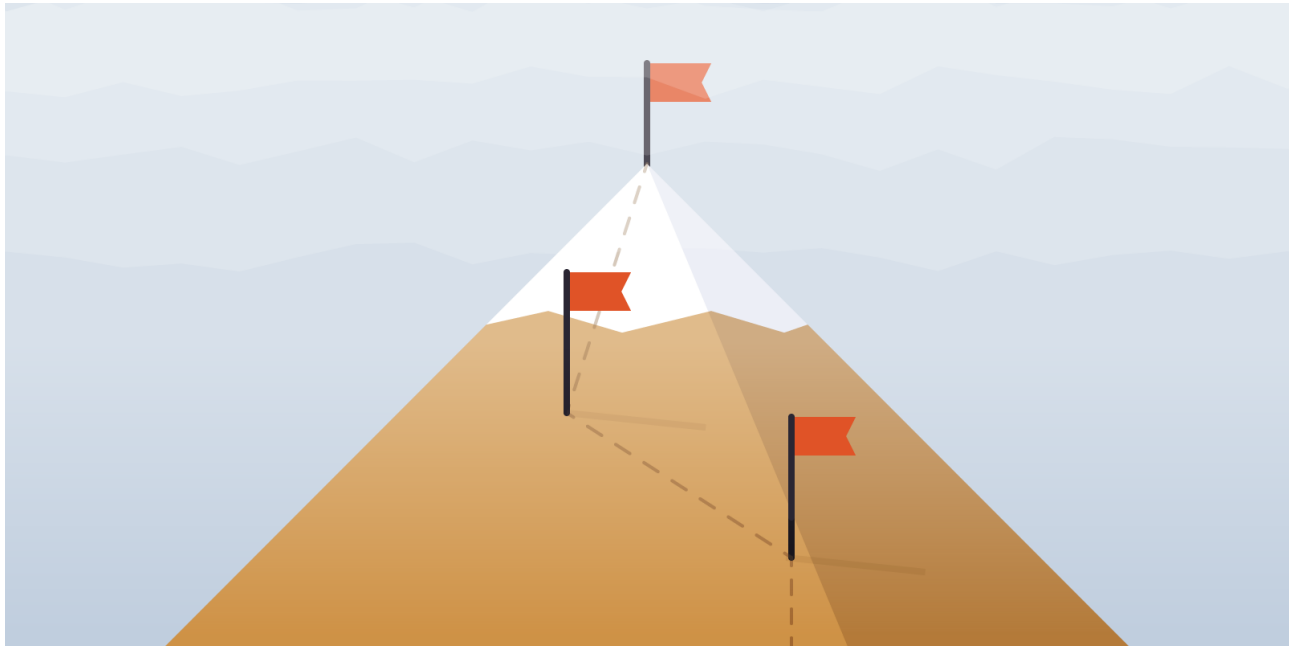
Tryon, et al. 2008 JAVMA

	Affected %		Carriers%		
	HYPP	PSSM	GBED	HERDA	LWF
AQHA	1.5	11.3	11.0	3.5	No
Paint	4.5	4.5	3.9	1.7	21.3
Halter	56.4	28.2	5.1	0.8	No
W pl	1.1	8.6	26.3	12.8	No
Cut	No	6.7	13.6	28.3	No
Rein	No	4.3	3.1	9.3	No
W cow	No	5.7	9.5	11.5	No
Barrel	1.2	1.4	1.2	1.2	No
Race	No	2.0	No	No	No

Courtesy of Dr. Sharon Spier, UC Davis

GENETIC COUNSELING

The goal of genetic counseling is to control genetic disorders and to propagate superior genes



RISK EVALUATION

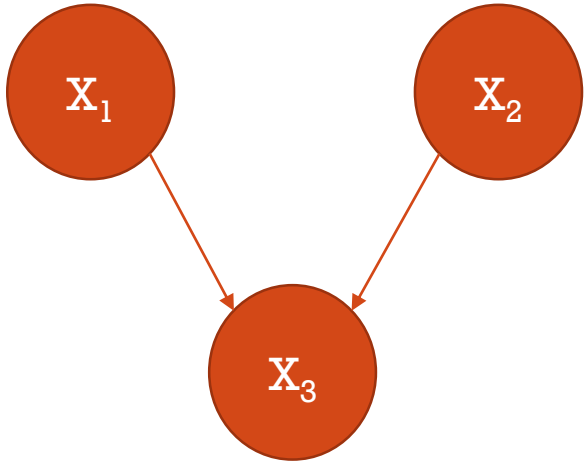
Risk:

- probability of occurence
- magnitude of impact

Likelihood	Impact				
	Insignificant	Minor	Moderate	Major	Severe
Almost certain	Moderate	High	High	Extreme	Extreme
Likely	Moderate	Moderate	High	High	Extreme
Possible	Low	Moderate	Moderate	High	Extreme
Unlikely	Low	Moderate	Moderate	Moderate	High
Rare	Low	Low	Moderate	Moderate	High

PROBABILITY OF OCCURENCE

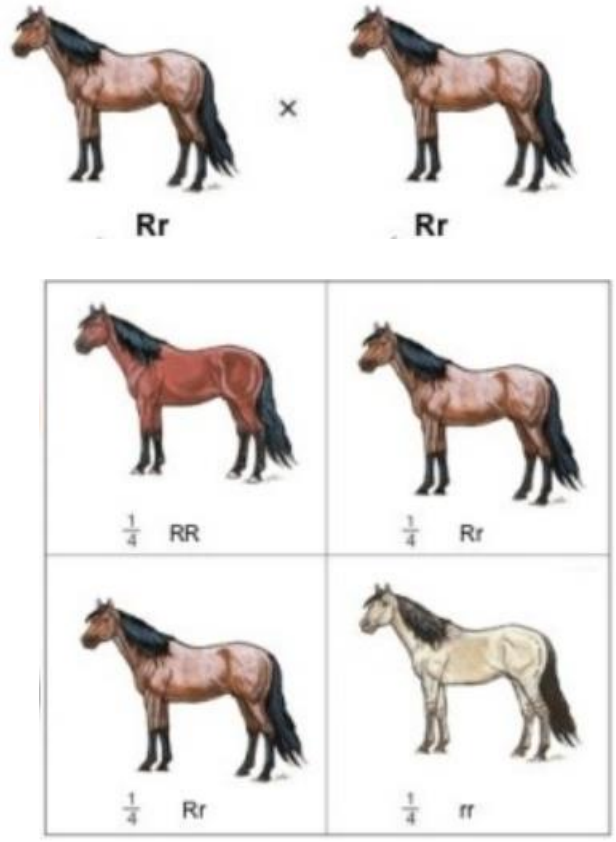
Bayes network:



Directed acyclic graph

Conditional probability table

X_1	X_2	AA	Aa	aa
AA	AA	100	0	0
Aa	Aa	25	50	25
AA	aa	0	50	50
…				



PROBABILITY OF OCCURENCE

Mendelian inheritance patterns:

The Genetics of Glaucoma, Cataracts, and Corneal Dystrophies

ALESSANDRO IANNACCONE, MD, MS, STEVEN R. SARKISIAN, JR., MD, NATALIE C. KERR, MD, FACS, AND WILLIAM R. MORRIS, MD

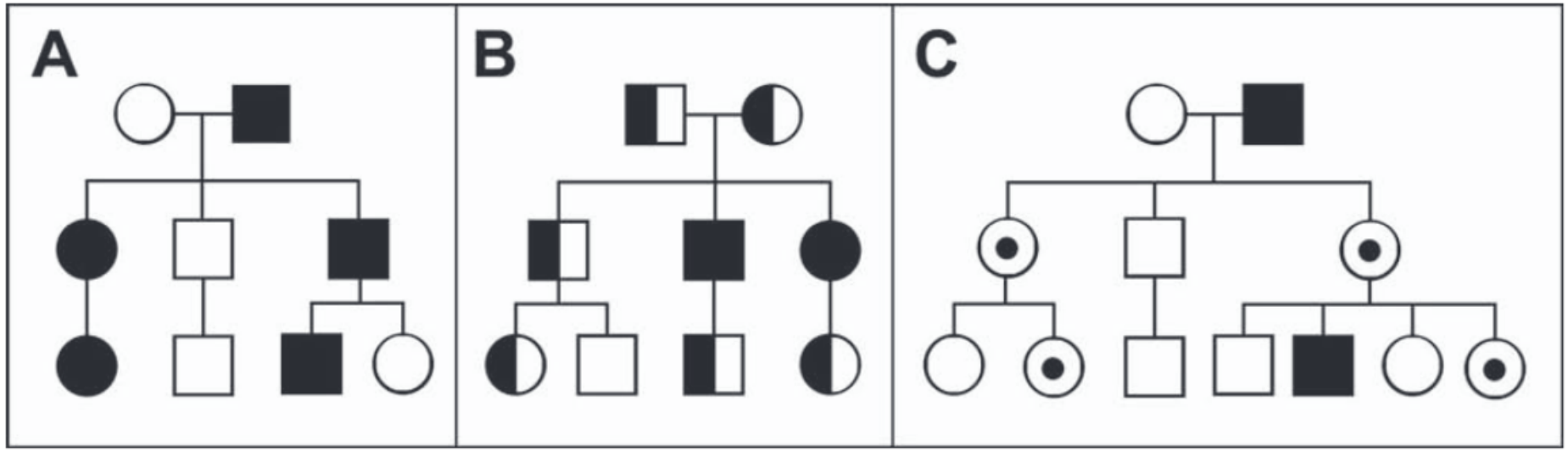
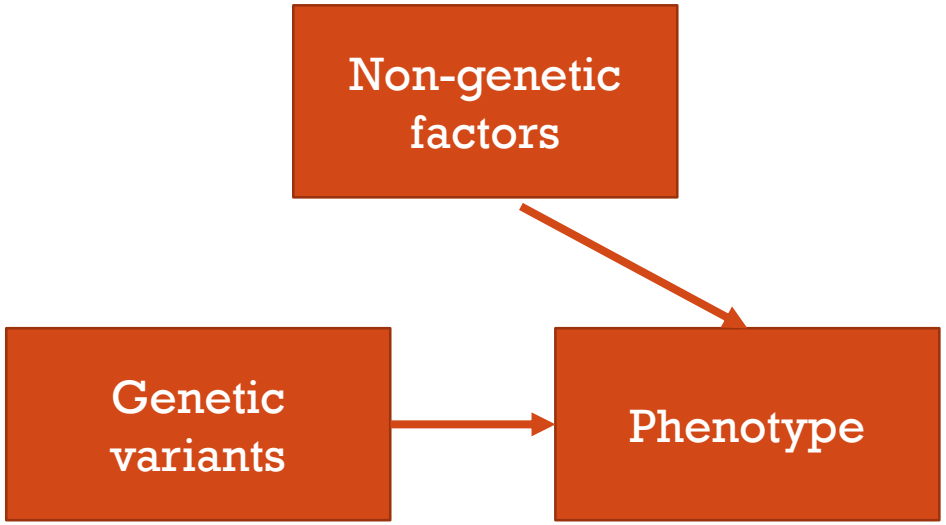


Fig. 1. Examples of pedigrees with classical Mendelian inheritance patterns. *A*: Autosomal dominant (AD or ad) inheritance. The filled symbols are affected heterozygotes. *B*: Autosomal recessive (AR or ar) inheritance. The filled symbols represent affected homozygotes or compound heterozygotes. The half-filled symbols identify heterozygote unaffected carriers. *C*: X-linked recessive (XL or xL) inheritance. The filled square symbols represent affected male hemizygotes. Carrier females are identified by the round target-like symbols.

PROBABILITY OF OCCURENCE

Non genetic risk factors:



Reduced (or incomplete) penetrance

Mutations in *DMRT3* affect locomotion in horses and spinal circuit function in mice

Lisa S. Andersson, Martin Larhammar, Fatima Memic, Hanna Wootz, Doreen Schwochow, Carl-Johan Rubin, Kalicharan Patra, Thorvaldur Arnason, Lisbeth Wellbring, Göran Hjälm, Freyja Imsland, Jessica L. Petersen, Molly E. McCue, James R. Mickelson, Gus Cothran, Nadav Ahituv, Lars Roepstorff, Sofia Mikko, Anna Vallstedt, Gabriella Lindgren, Leif Andersson ✉ & Klas Kullander

Icelandic horse

Two-beat gait

Trot

MAGNITUDE OF IMPACT

Utility: owner's satisfaction

Market value

https://myexracer.com/

- purchase price
- age and health of the animal
- breeding status, pedigree
- special training
- veterinary expenses

Emotional value

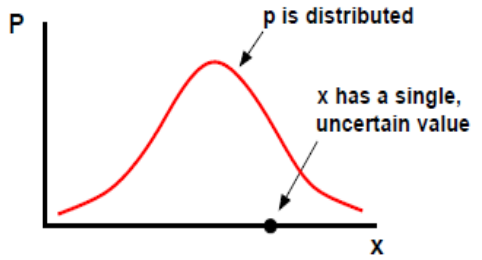
https://www.pinterest.fr

UNCERTAINTY

Prior probability:

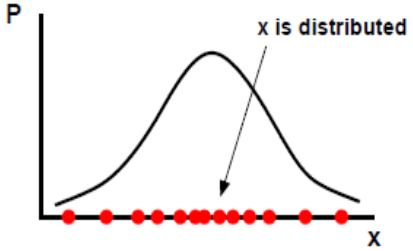
Bayesian

Probability *quantifies uncertainty* in an inductive inference. $p(x)$ describes how *probability* is distributed over the possible values x might have taken



Frequentist

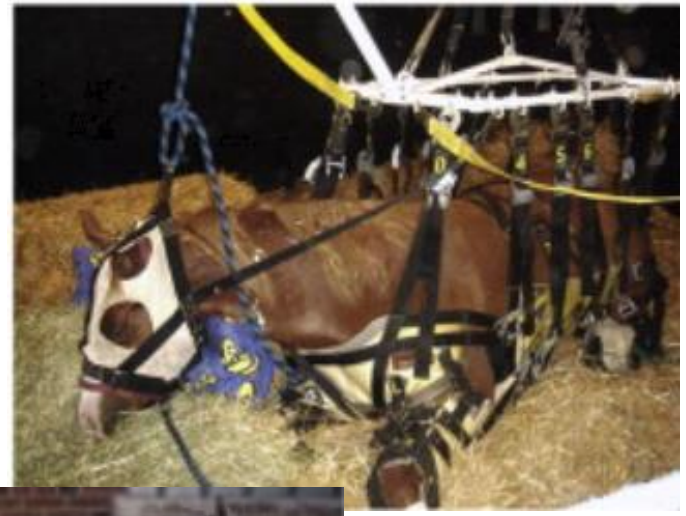
Probabilities are always (limiting) rates/proportions/frequencies that *quantify variability* in a sequence of trials. $p(x)$ describes how the *values of x* would be distributed among infinitely many trials:



EXAMPLE: POLYSACCHARIDE STORAGE MYOPATHY, TYPE 1

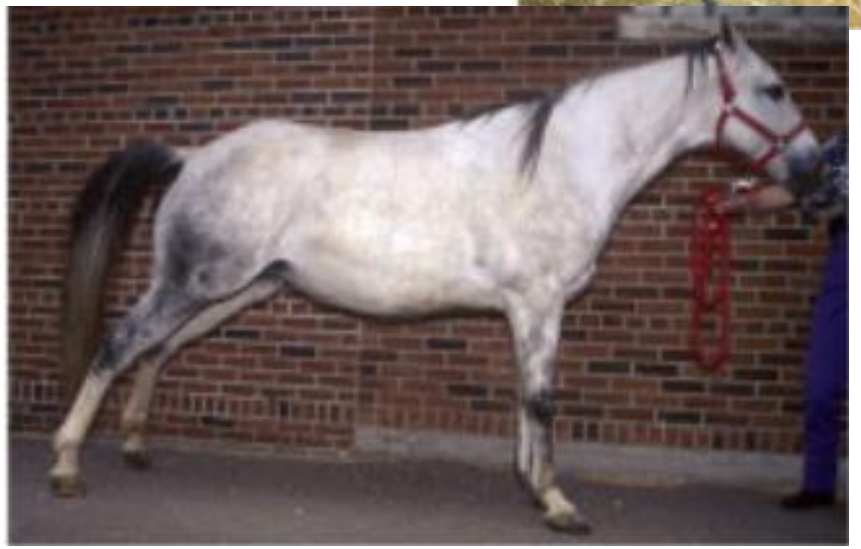
Glycogen synthase (*GYS1*) mutation causes a novel skeletal muscle glycogenosis ☆

Molly E. McCue [a], Stephanie J. Valberg [a], Michael B. Miller [b], Claire Wade [c], Salvatore DiMauro [d], Hasan O. Akman [d], James R. Mickelson [e]



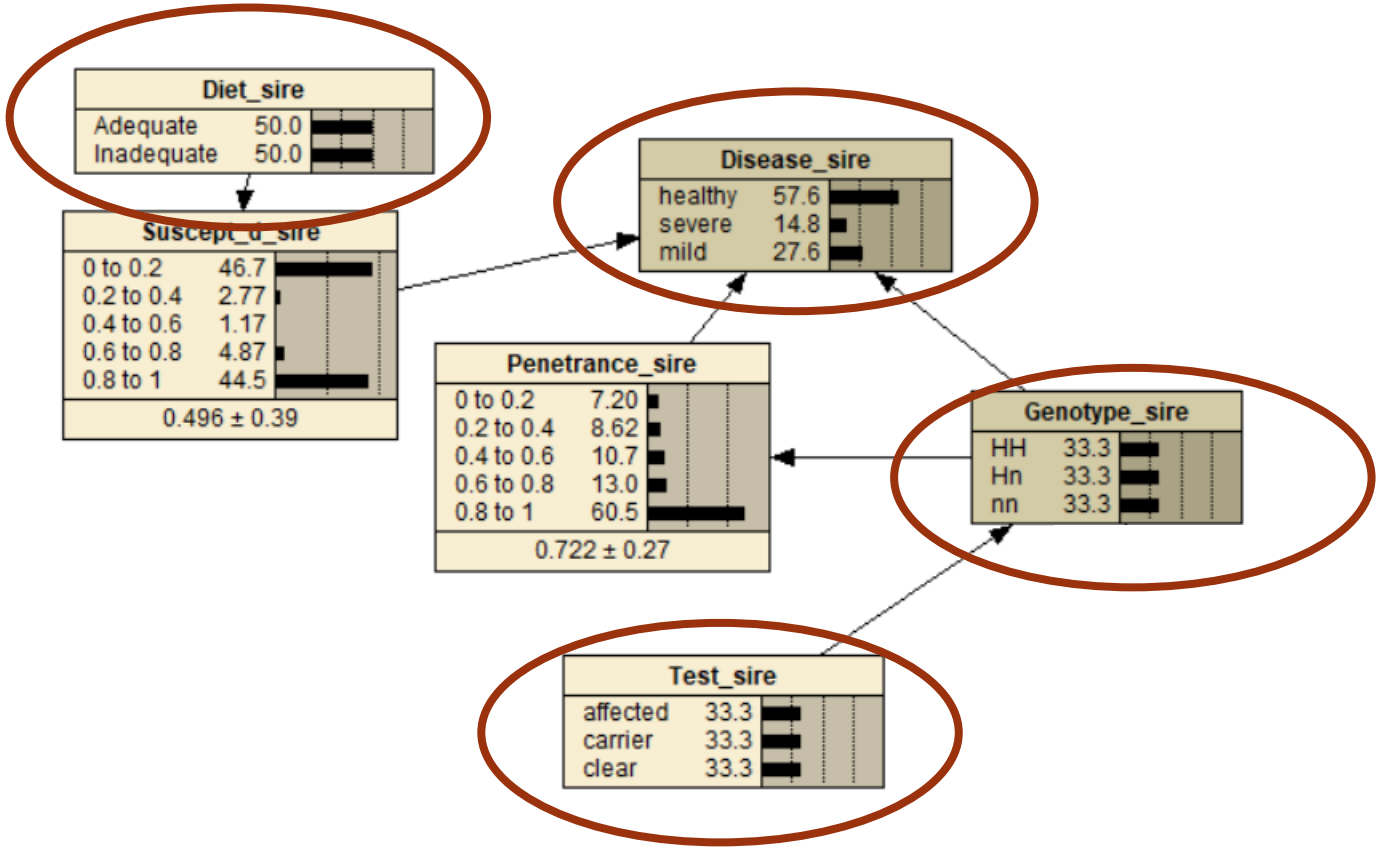
Clinical expression maybe subtle
- muscle pain and stiffness,
- back pain or muscle atrophy,

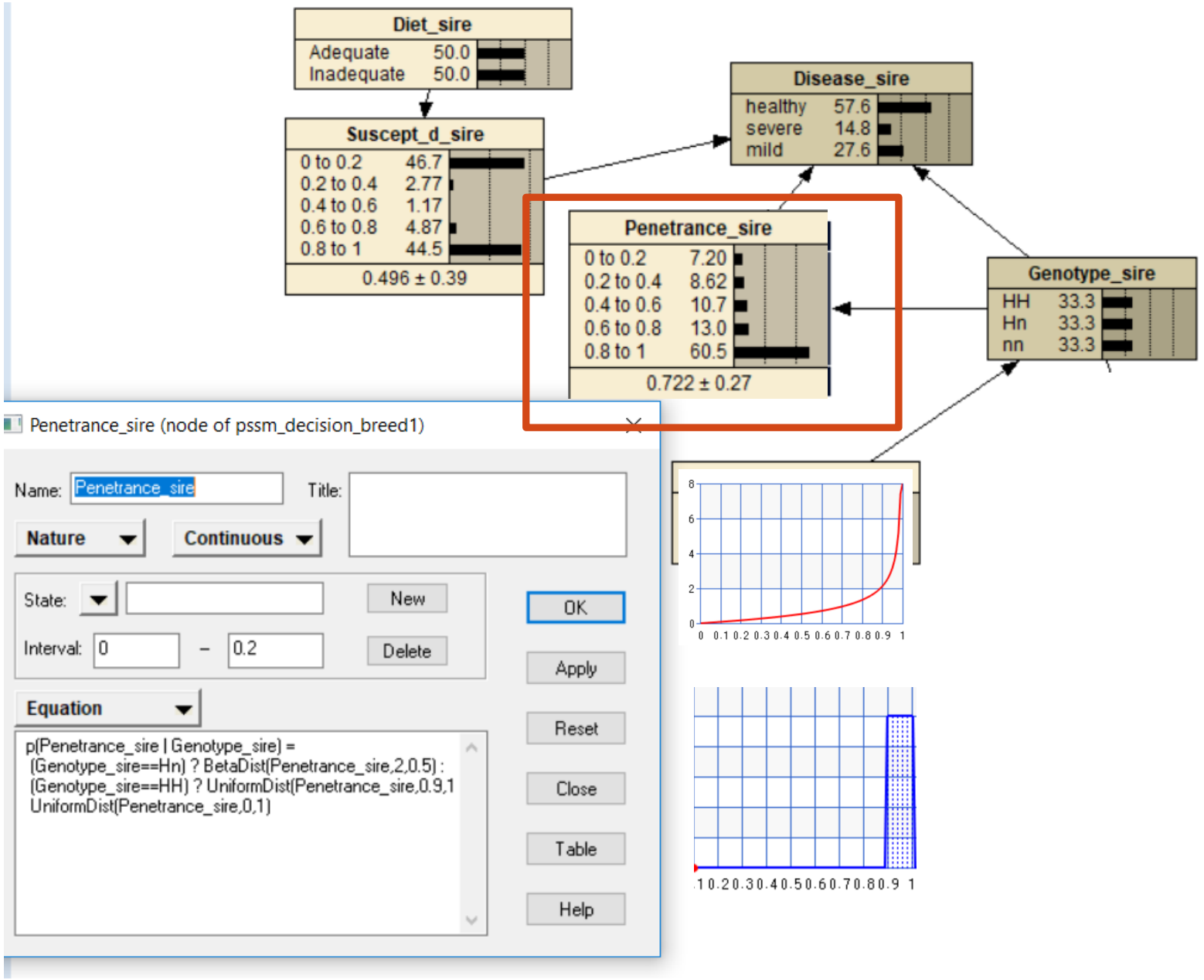
or severe
- lameness
- myoglobinuria
- progressive weakness

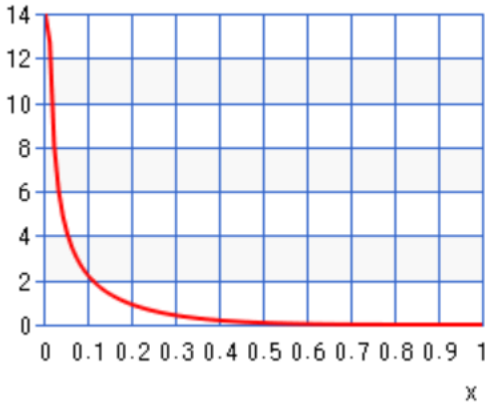


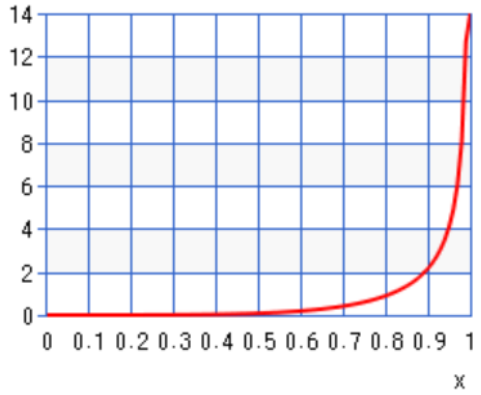
EXAMPLE: POLYSACCHARIDE STORAGE MYOPATHY, TYPE 1

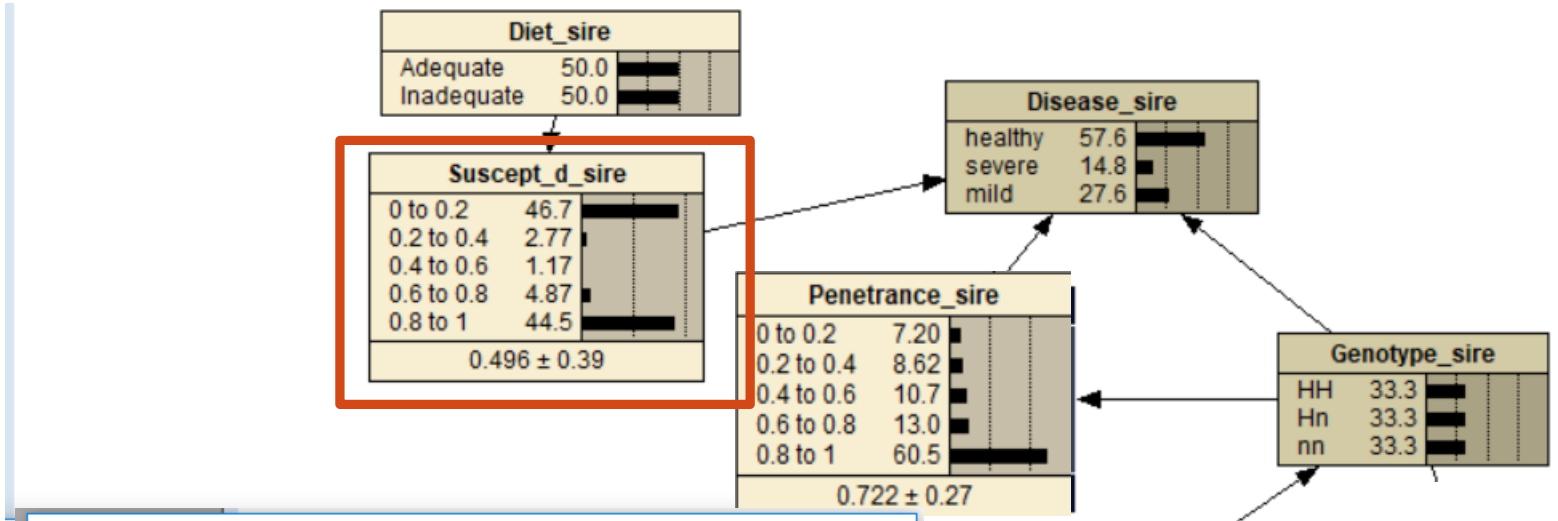
Autosomal dominant
Reduced penetrance (diet, exercise)
Genetic test available




Diet_sire
Adequate 50.0
Inadequate 50.0
Suscept_d_sire
0 to 0.2 46.7
0.2 to 0.4 2.77
0.4 to 0.6 1.17
0.6 to 0.8 4.87
0.8 to 1 44.5
0.496 ± 0.39
Disease_sire
healthy 57.6
severe 14.8
mild 27.6
Penetrance_sire
0 to 0.2 7.20
0.2 to 0.4 8.62
0.4 to 0.6 10.7
0.6 to 0.8 13.0
0.8 to 1 60.5
0.722 ± 0.27
Genotype_sire
HH 33.3
Hn 33.3
nn 33.3
Penetrance_sire (node of pssm_decision_breed1)
Name: Penetrance_sire
Title:
Nature
Continuous
State:
New
Interval: 0 – 0.2
Delete
Equation
p(Penetrance_sire | Genotype_sire) =
(Genotype_sire==Hn) ? BetaDist(Penetrance_sire,2,0.5) :
(Genotype_sire==HH) ? UniformDist(Penetrance_sire,0.9,1
UniformDist(Penetrance_sire,0,1)
OK
Apply
Reset
Close
Table
Help


14
12
10
8
6
4
2
0
0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1
x


14
12
10
8
6
4
2
0
0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1
x


Diet_sire
Adequate 50.0
Inadequate 50.0
Suscept_d_sire
0 to 0.2 46.7
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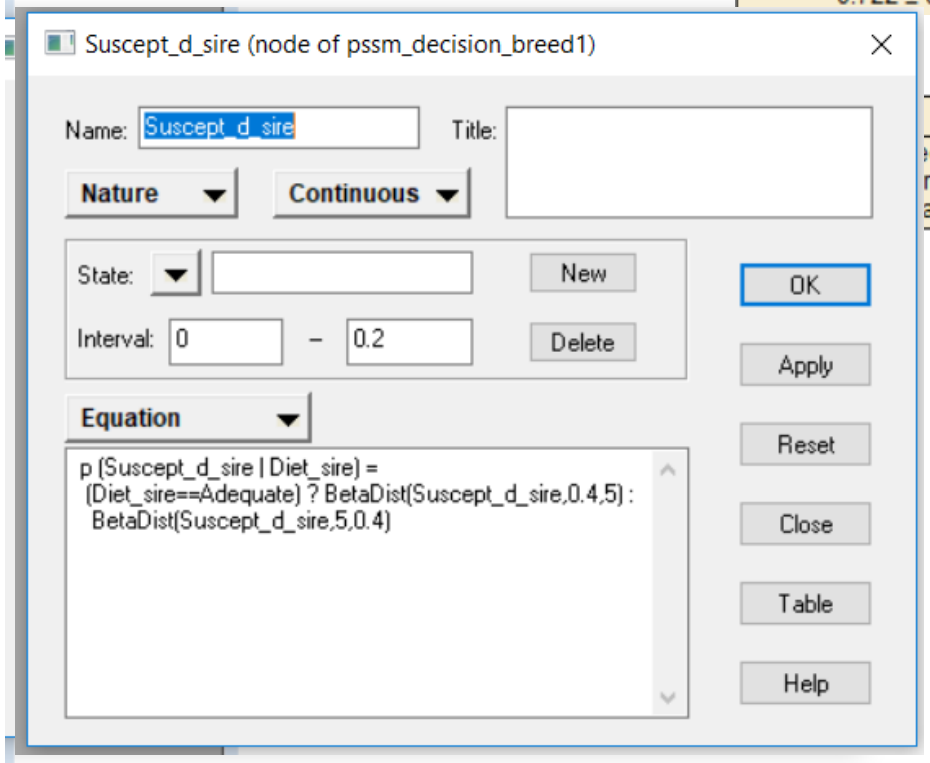
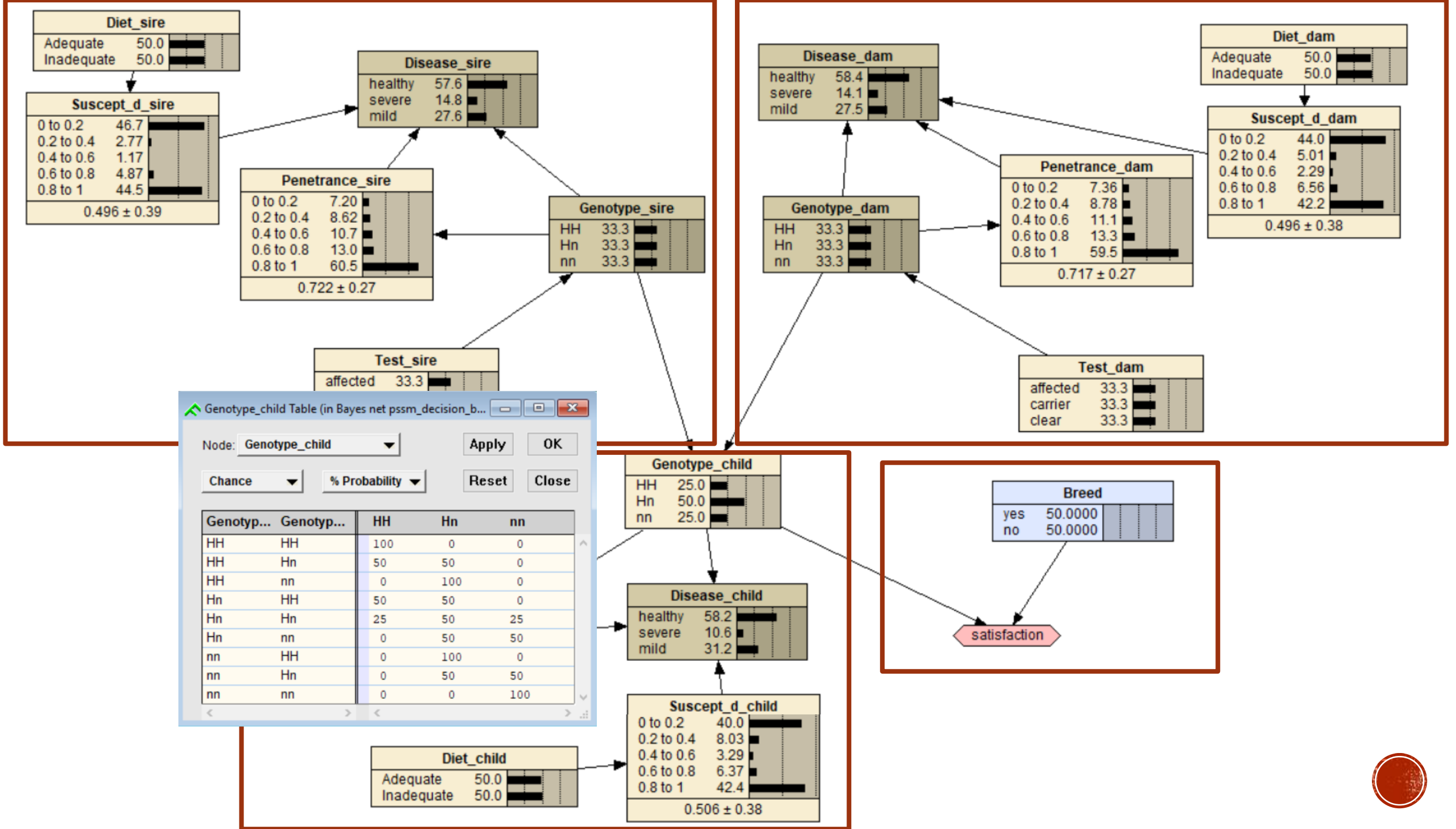
0.2 to 0.4 8.62
0.4 to 0.6 10.7
0.6 to 0.8 13.0
0.8 to 1 60.5
0.722 ± 0.27
Genotype_sire
HH 33.3
Hn 33.3
nn 33.3
Test_sire
33.3
33.3
33.3


Suscept_d_sire (node of pssm_decision_breed1)
Name: Suscept_d_sire
Title:
Nature
Continuous
State:
New
Interval: 0 – 0.2
Delete
Equation
p (Suscept_d_sire | Diet_sire) =
(Diet_sire==Adequate) ? BetaDist(Suscept_d_sire,0.4,5) :
BetaDist(Suscept_d_sire,5,0.4)
OK
Apply
Reset
Close
Table
Help


Diet_sire
Adequate 50.0
Inadequate 50.0
Suscept_d_sire
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0.2 to 0.4 2.77
0.4 to 0.6 1.17
0.6 to 0.8 4.87
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mild 27.6
Penetrance_sire
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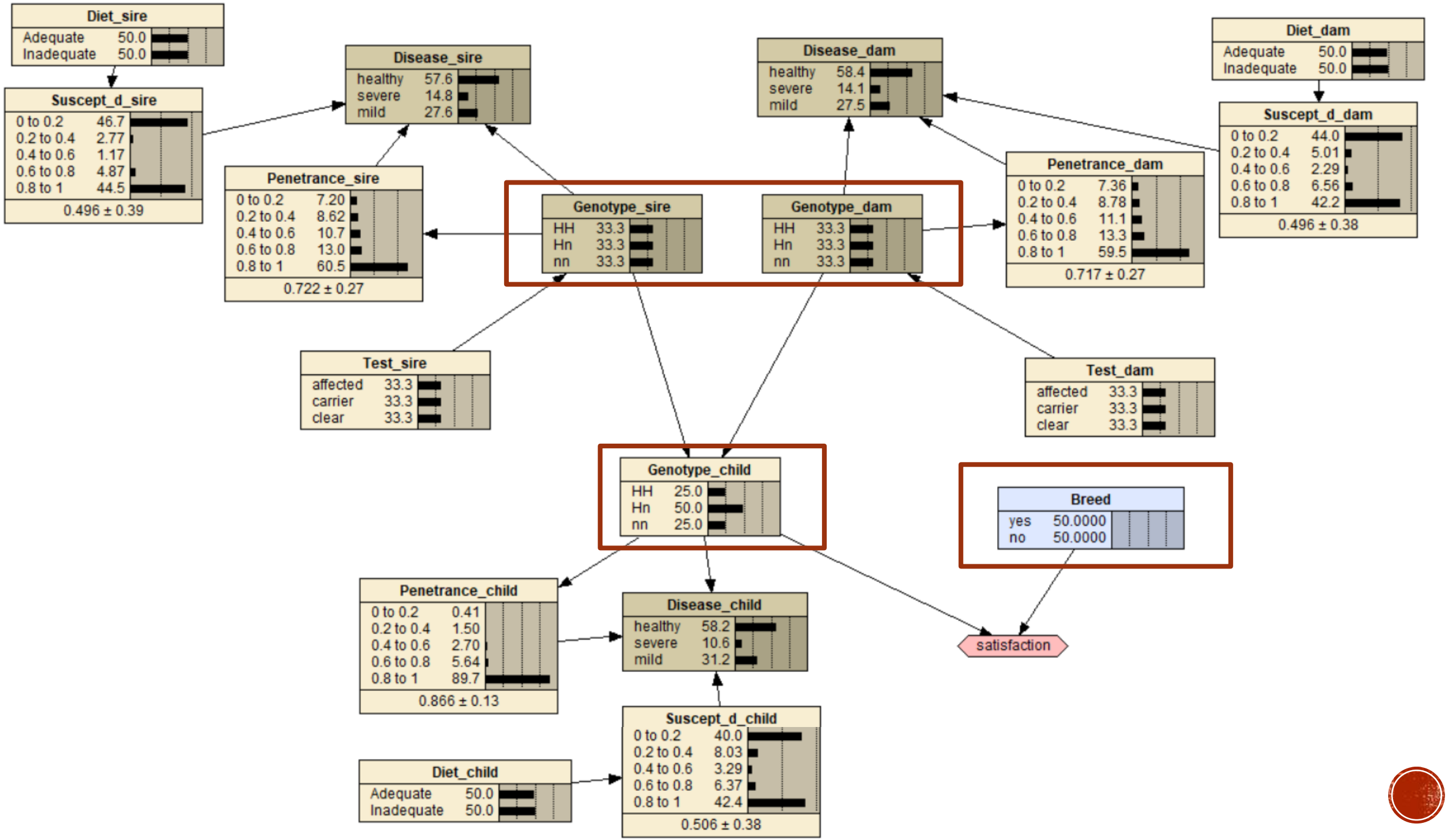
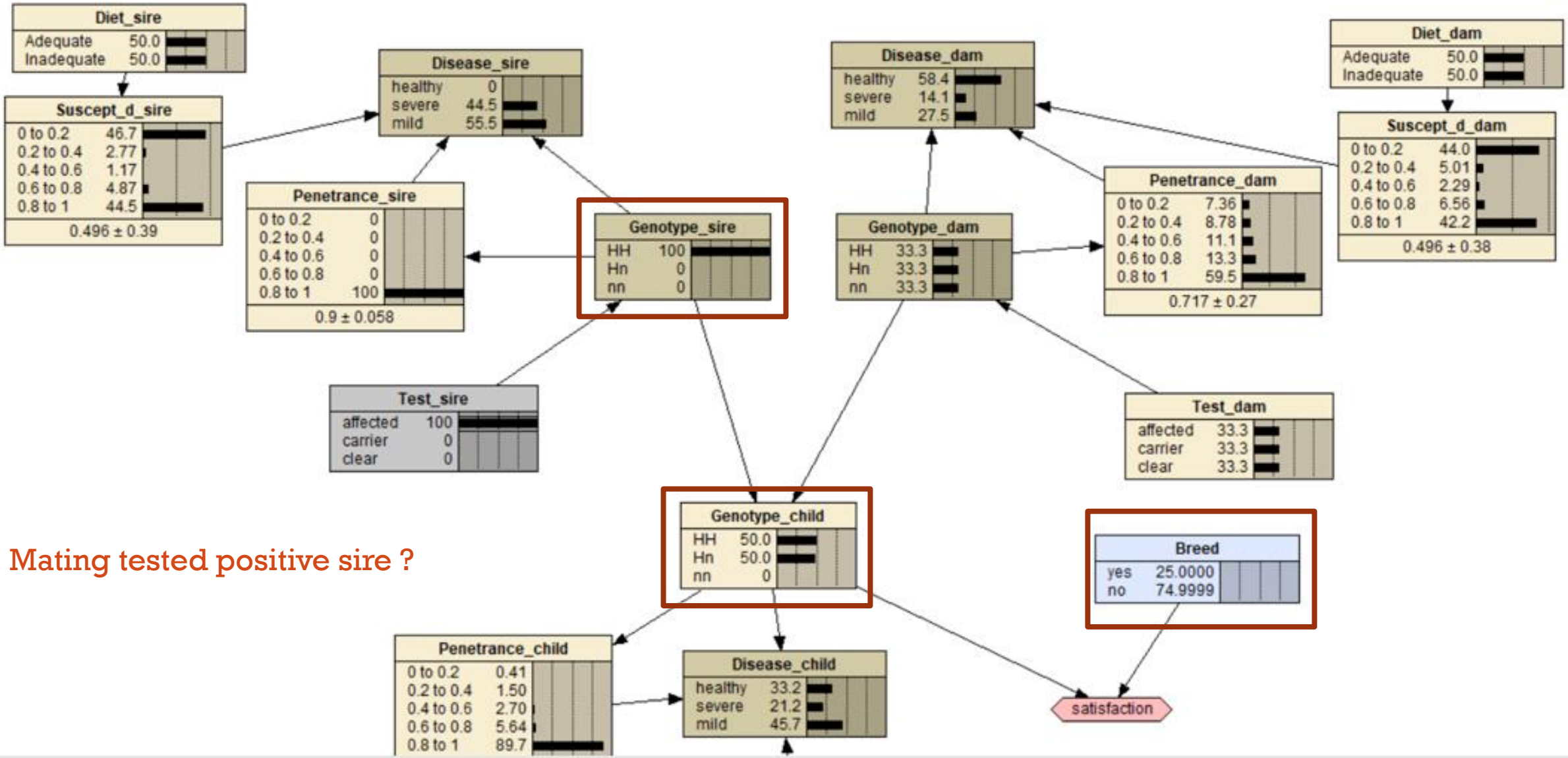
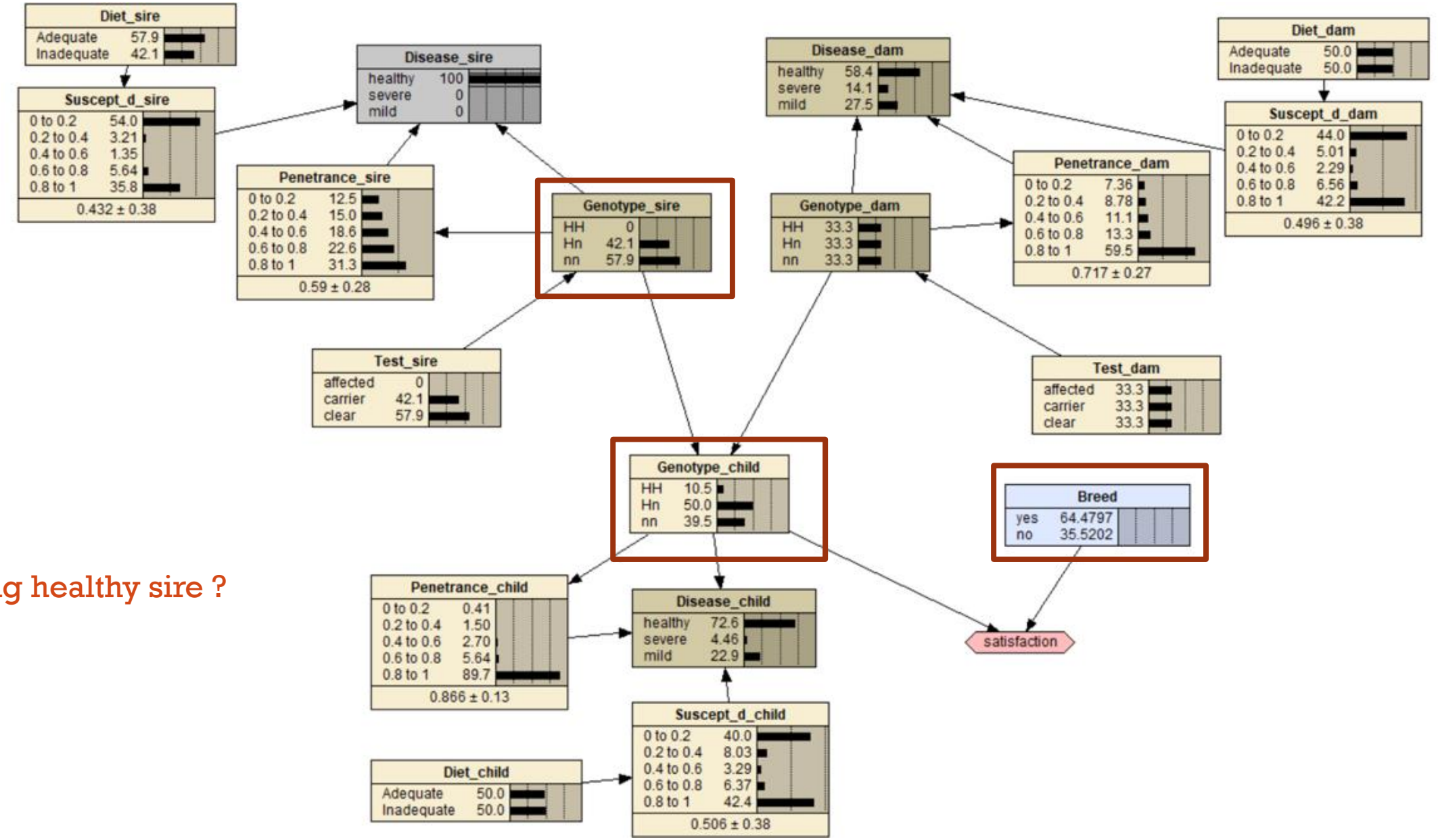
0.2 to 0.4 8.62
0.4 to 0.6 10.7
0.6 to 0.8 13.0
0.8 to 1 60.5
0.722 ± 0.27
Genotype_sire
HH 33.3
Hn 33.3
nn 33.3
Test_sire
affected 33.3
Disease_dam
healthy 58.4
severe 14.1
mild 27.5
Diet_dam
Adequate 50.0
Inadequate 50.0
Suscept_d_dam
0 to 0.2 44.0
0.2 to 0.4 5.01
0.4 to 0.6 2.29
0.6 to 0.8 6.56
0.8 to 1 42.2
0.496 ± 0.38
Penetrance_dam
0 to 0.2 7.36
0.2 to 0.4 8.78
0.4 to 0.6 11.1
0.6 to 0.8 13.3
0.8 to 1 59.5
0.717 ± 0.27
Genotype_dam
HH 33.3
Hn 33.3
nn 33.3
Test_dam
affected 33.3
carrier 33.3
clear 33.3
Genotype_child Table (in Bayes net pssm_decision_b...
Node: Genotype_child
Apply
OK
Chance
% Probability
Reset
Close
Genotyp... Genotyp... HH Hn nn
HH HH 100 0 0
HH Hn 50 50 0
HH nn 0 100 0
Hn HH 50 50 0
Hn Hn 25 50 25
Hn nn 0 50 50
nn HH 0 100 0
nn Hn 0 50 50
nn nn 0 0 100
Genotype_child
HH 25.0
Hn 50.0
nn 25.0
Disease_child
healthy 58.2
severe 10.6
mild 31.2
Suscept_d_child
0 to 0.2 40.0
0.2 to 0.4 8.03
0.4 to 0.6 3.29
0.6 to 0.8 6.37
0.8 to 1 42.4
0.506 ± 0.38
Diet_child
Adequate 50.0
Inadequate 50.0
Breed
yes 50.0000
no 50.0000
satisfaction

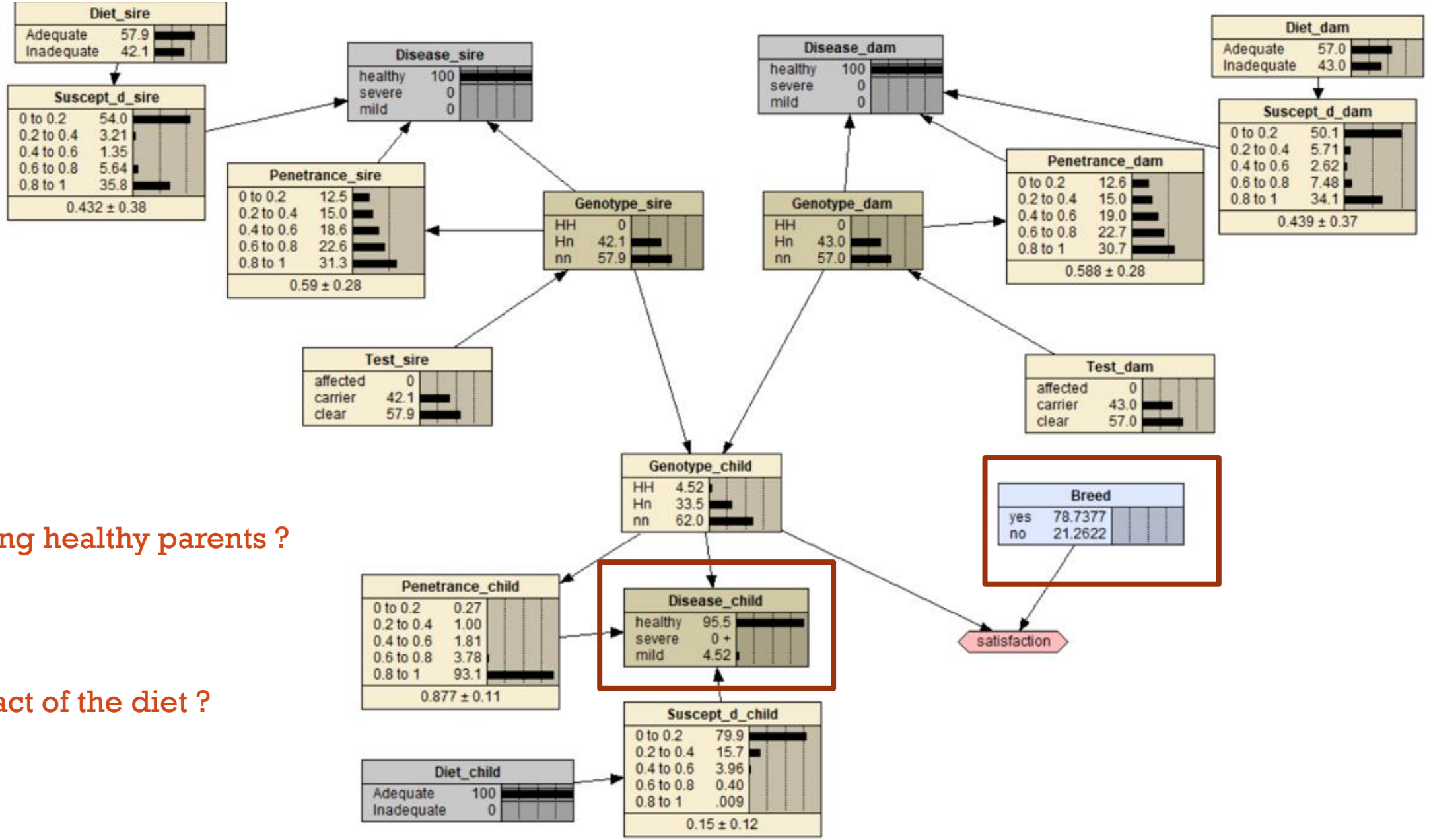

Diet_sire
Adequate 50.0
Inadequate 50.0
Suscept_d_sire
0 to 0.2 46.7
0.2 to 0.4 2.77
0.4 to 0.6 1.17
0.6 to 0.8 4.87
0.8 to 1 44.5
0.496 ± 0.39
Disease_sire
healthy 57.6
severe 14.8
mild 27.6
Penetrance_sire
0 to 0.2 7.20
0.2 to 0.4 8.62
0.4 to 0.6 10.7
0.6 to 0.8 13.0
0.8 to 1 60.5
0.722 ± 0.27
Genotype_sire
HH 33.3
Hn 33.3
nn 33.3
Genotype_dam
HH 33.3
Hn 33.3
nn 33.3
Disease_dam
healthy 58.4
severe 14.1
mild 27.5
Diet_dam
Adequate 50.0
Inadequate 50.0
Suscept_d_dam
0 to 0.2 44.0
0.2 to 0.4 5.01
0.4 to 0.6 2.29
0.6 to 0.8 6.56
0.8 to 1 42.2
0.496 ± 0.38
Penetrance_dam
0 to 0.2 7.36
0.2 to 0.4 8.78
0.4 to 0.6 11.1
0.6 to 0.8 13.3
0.8 to 1 59.5
0.717 ± 0.27
Test_sire
affected 33.3
carrier 33.3
clear 33.3
Test_dam
affected 33.3
carrier 33.3
clear 33.3
Genotype_child
HH 25.0
Hn 50.0
nn 25.0
Breed
yes 50.0000
no 50.0000
Penetrance_child
0 to 0.2 0.41
0.2 to 0.4 1.50
0.4 to 0.6 2.70
0.6 to 0.8 5.64
0.8 to 1 89.7
0.866 ± 0.13
Disease_child
healthy 58.2
severe 10.6
mild 31.2
satisfaction
Diet_child
Adequate 50.0
Inadequate 50.0
Suscept_d_child
0 to 0.2 40.0
0.2 to 0.4 8.03
0.4 to 0.6 3.29
0.6 to 0.8 6.37
0.8 to 1 42.4
0.506 ± 0.38



Mating tested positive sire ?

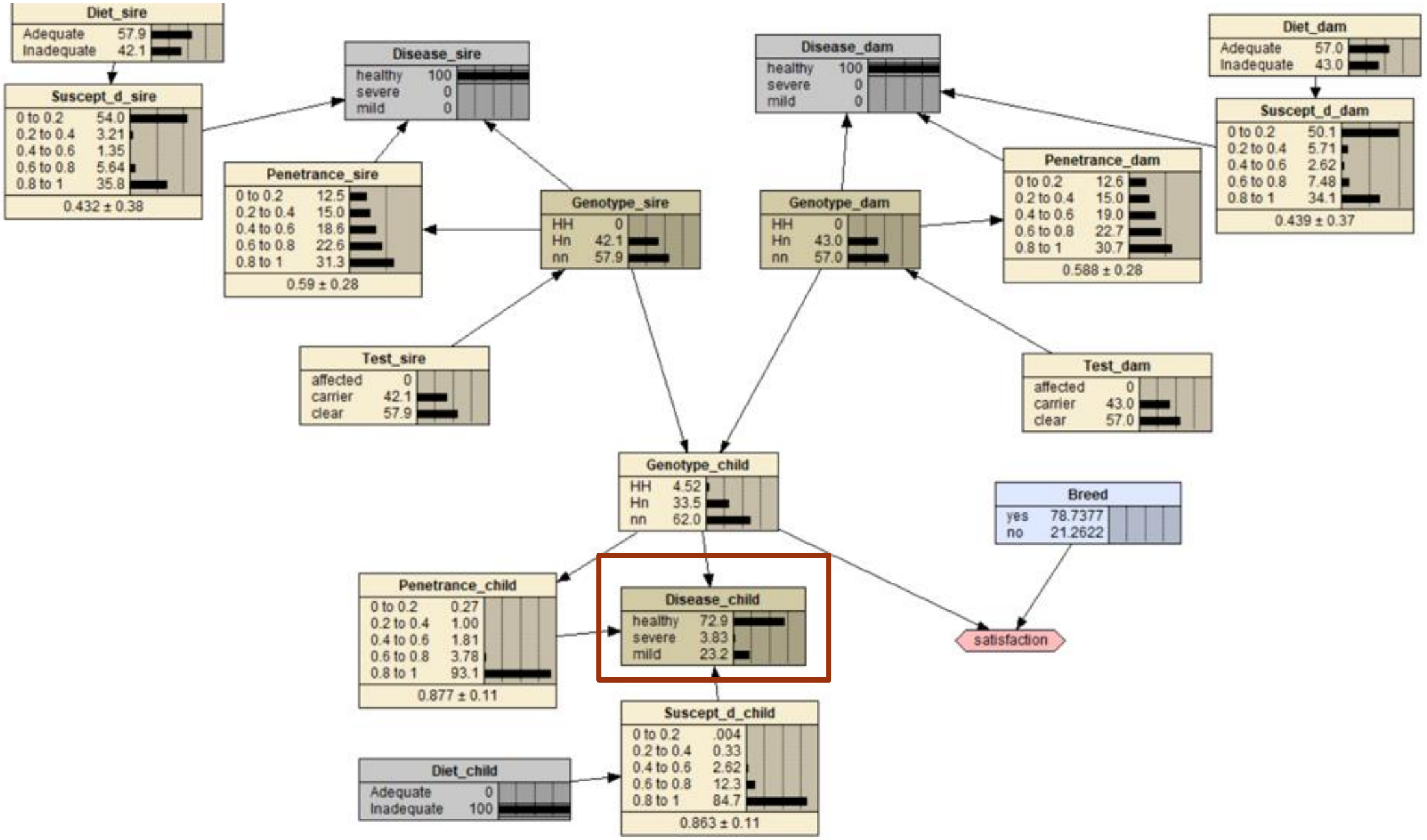


Mating healthy sire ?



Mating healthy parents ?

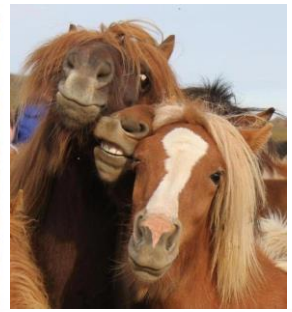
Impact of the diet ?


Diet_sire
Adequate 57.9
Inadequate 42.1
Suscept_d_sire
0 to 0.2 54.0
0.2 to 0.4 3.21
0.4 to 0.6 1.35
0.6 to 0.8 5.64
0.8 to 1 35.8
0.432 ± 0.38
Disease_sire
healthy 100
severe 0
mild 0
Penetrance_sire
0 to 0.2 12.5
0.2 to 0.4 15.0
0.4 to 0.6 18.6
0.6 to 0.8 22.6
0.8 to 1 31.3
0.59 ± 0.28
Genotype_sire
HH 0
Hn 42.1
nn 57.9
Test_sire
affected 0
carrier 42.1
clear 57.9
Disease_dam
healthy 100
severe 0
mild 0
Diet_dam
Adequate 57.0
Inadequate 43.0
Suscept_d_dam
0 to 0.2 50.1
0.2 to 0.4 5.71
0.4 to 0.6 2.62
0.6 to 0.8 7.48
0.8 to 1 34.1
0.439 ± 0.37
Penetrance_dam
0 to 0.2 12.6
0.2 to 0.4 15.0
0.4 to 0.6 19.0
0.6 to 0.8 22.7
0.8 to 1 30.7
0.588 ± 0.28
Genotype_dam
HH 0
Hn 43.0
nn 57.0
Test_dam
affected 0
carrier 43.0
clear 57.0
Genotype_child
HH 4.52
Hn 33.5
nn 62.0
Breed
yes 78.7377
no 21.2622
Penetrance_child
0 to 0.2 0.27
0.2 to 0.4 1.00
0.4 to 0.6 1.81
0.6 to 0.8 3.78
0.8 to 1 93.1
0.877 ± 0.11
Disease_child
healthy 72.9
severe 3.83
mild 23.2
satisfaction
Suscept_d_child
0 to 0.2 .004
0.2 to 0.4 0.33
0.4 to 0.6 2.62
0.6 to 0.8 12.3
0.8 to 1 84.7
0.863 ± 0.11
Diet_child
Adequate 0
Inadequate 100

GENETIC COUNSELING

GOING FURTHER

- MOOC on genetic counseling
- Facebook page on issue in genetics
- Program for the vets and owners
- More complicated situations



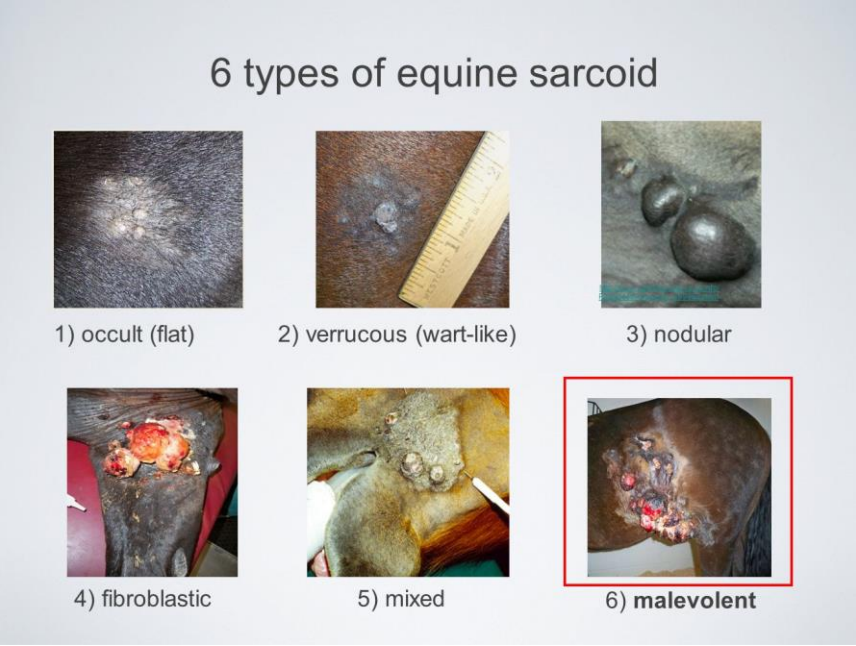
Genetic counseling for animals

The science for healthy and performing animals

GeneticCounseling@ulg.ac.be

COMPLEXITY

Inheritance pattern (incomplete penetrance, variable expressivity, …)

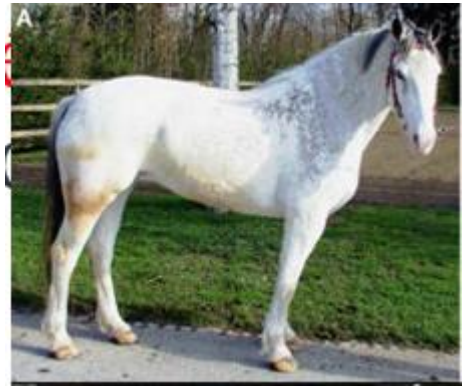


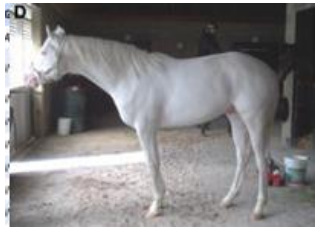
COMPLEXITY

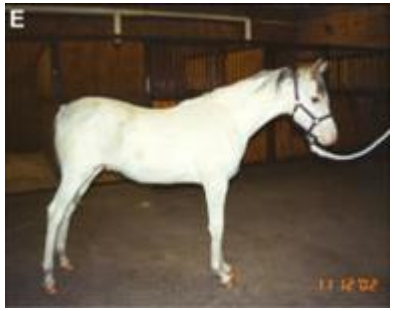
Alellic heterogeneity

Génotypes *KIT* et phénotypes

Allele	Breed	Origination	Characteristics
W1	FM	*Cigale*, 1957	*Usually pure white; nonsense mutation at exon 15, truncation 15-21*
W2	TB	*KY Colonel*, 1946	*Usually pure white; substitution Glycine-Arginn exon 13*
W3	AR	*R Khasper*, 1996	*Usually pure white; nonsense mutation at exon 4, truncation 4-21*
W4	CW	*Sultan*, 1912	*White, substitution Glycine-Arginin in exon 12*
W5	TB	*Puchilingui*, 1984	*White to sabino-like; deletion in exon 15 and premature stop codo*
W6	TB	*not published*	*White, substitution Glycine-Arginin exon 5-21*
W7	TB	*not published*	*White, splice site of intron 2*
W8	IH	*not published*	*Partially white (sabino-like), splice site mutation of intron15*
W9	HH	*not published*	*White, missense mutation in exon 12*
W10	QH	*GQ Sunlana*, 2000	*Exhibit a wide range of phenotypes similar to that of W5, deletion exon 7and premature stop codon*
W11	SGDH	*not published*	*Complety white, splice site mutation of intron 20)*
W12	TB	*not published*	*Partially white, deletion in exon 3*
W13	QHxPP	*not published*	*White, splice site mutation of intron 17*
W14	TB	*not published*	*White, deletion in exon 17*
W15	AR	*not published*	*Partially white (sabino-like), missense mutation in exon*
W16	OL	*not published*	*White, missense mutation in exon 7*
W17	JD	*not published*	*White*
W18	CH	*not published*	*Pronounced depigmentation phenotype, sabino-like, mutation in intron 8 (c.1346 + 1G>A)*
W19	PB	*not published*	*Partially white, missense variant in exon 8 (c.1322A>G; p.Tyr441Cys)*
W20	TB + *other breeds*	*not published*	*Partially white, missense variant in exon 14 (c.2045G>A; p.Arg682His). Subtle effect on pigmentation (white pattern); not homozygous lethal.* Voir aussi *W20 project*
W21	IH	*not published*	*White-spotted coat colour phenotype and heterochromia iridis exon 17 (c.2369delC)*
			White-spotted coat colour phenotype. Degree of depigmentation in

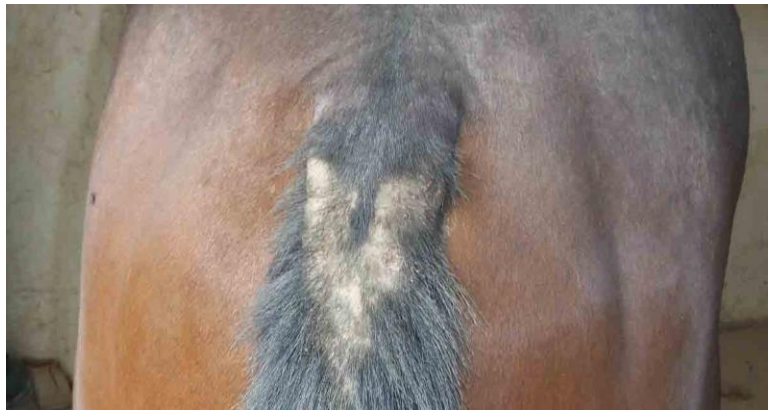


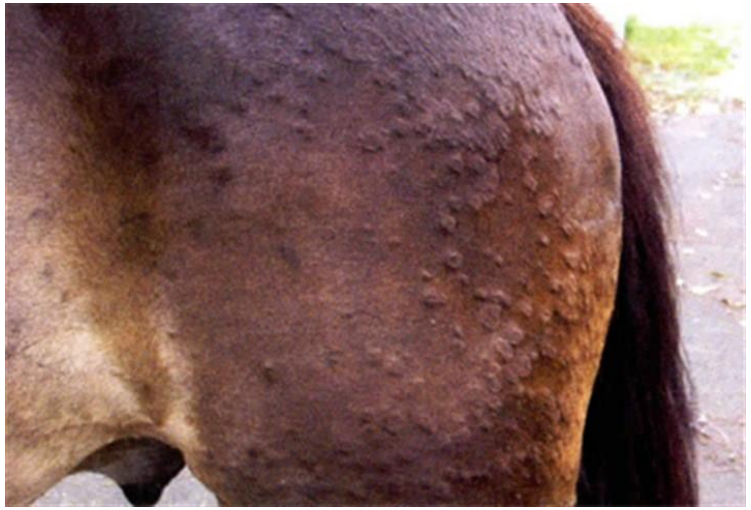




COMPLEXITY

Interaction genetic X environment





COMPLEXITY

Polygenic and non-genetic factors

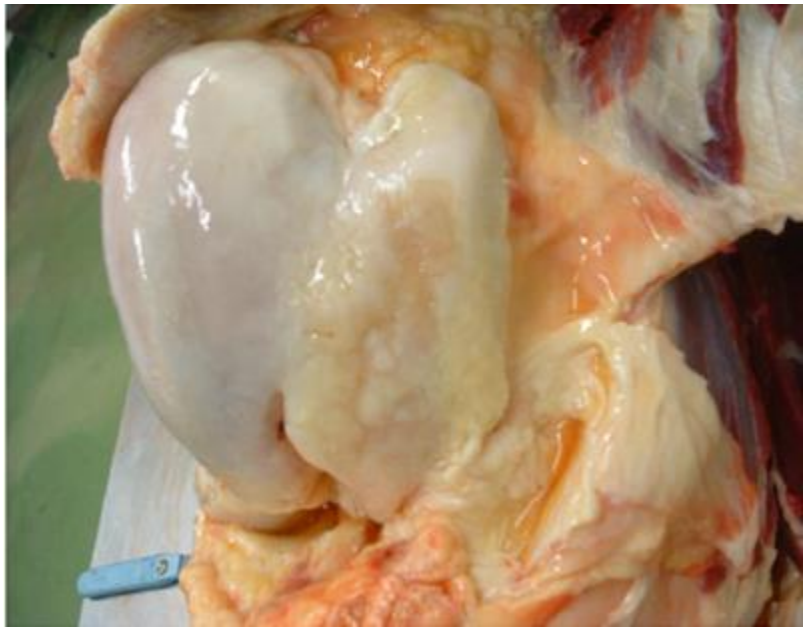


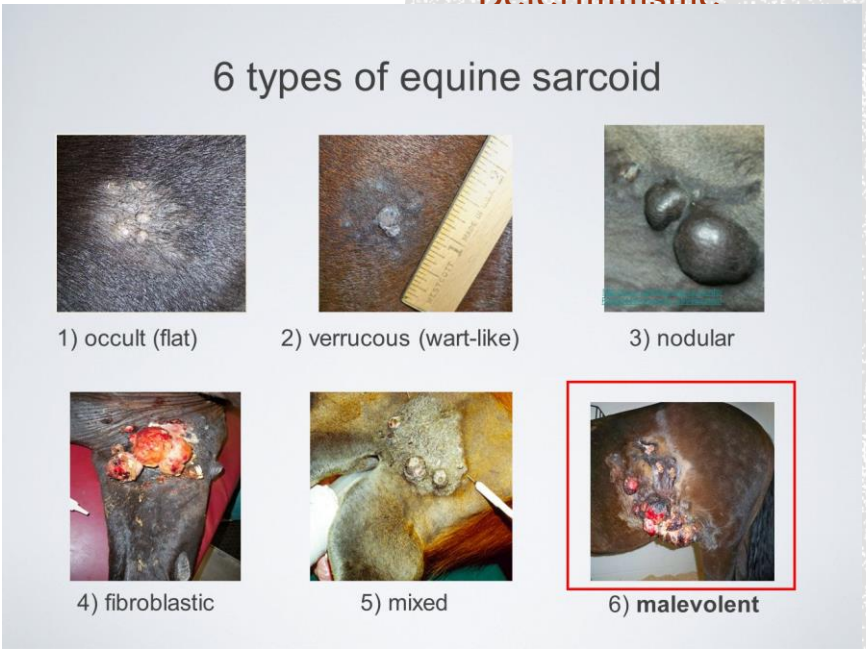
figure 14).

Déterminisme génétique

1/Simple

- Autosomique dominant

<u>Pénétrance incomplète</u> (Ex: Sarcoïdes et ELA)



jdetilleux@ulg.ac.be

Déterminisme génétique

2/Complexe

Hétérogénéité allélique

Ex. Blanc dominant

Génotypes *KIT* et phénotypes

Allele	*Breed*	*Origination*	*Characteristics*
W1	FM	*Cigale*, 1957	*Usually pure white; nonsense mutation at exon 15, truncation 15-21*
W2	TB	*KY Colonel*, 1946	*Usually pure white; substitution Glycine-Arginn exon 13*
W3	AR	*R Khasper*, 1996	*Usually pure white; nonsense mutation at exon 4, truncation 4-21*
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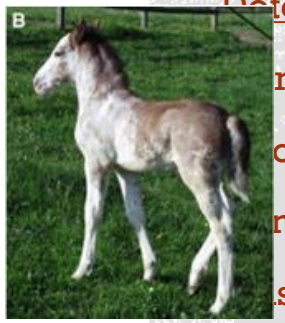
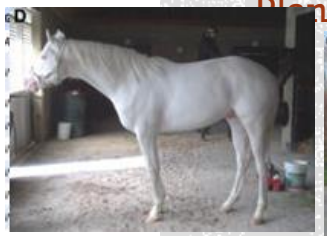
W7	TB	*not published*	*White, splice site of intron 2*
W8	IH	*not published*	*Partially white (sabino-like), splice site mutation of intron15*
W9	HH	*not published*	*White, missense mutation in exon 12*
W10	QH	*GQ Suntania*, 2000	*Exhibit a wide range of phenotypes similar to that of W5, deletion exon 7and premature stop codon*
W11	SGDH	*not published*	*Complety white, splice site mutation of intron 20)*
W12	TB	*not published*	*Partially white, deletion in exon 3*
W13	QHxPP	*not published*	*White, splice site mutation of intron 17*
W14	TB	*not published*	*White, deletion in exon 17*
W15	AR	*not published*	*Partially white (sabino-like), missense mutation in exon*
W16	OL	*not published*	*White, missense mutation in exon 7*
W17	JD	*not published*	*White*
W18	CH	*not published*	*Pronounced depigmentation phenotype, sabino-like, mutation in intron 8 (c.1346 + 1G>A)*
W19	PB	*not published*	*Partially white, missense variant in exon 8 (c.1322A>G; p.Tyr441Cys)*
W20	TB + *other breeds*	*not published*	*Partially white, missense variant in exon 14 (c.2045G>A; p.Arg682His). Subtle effect on pigmentation (white pattern); not homozygous lethal.* Voir aussi *W20 project*
W21	IH	*not published*	*White-spotted coat colour phenotype and heterochromia iridis exon 17 (c.2369delC)*
			White-spotted coat colour phenotype. Degree of depigmentation in

UE





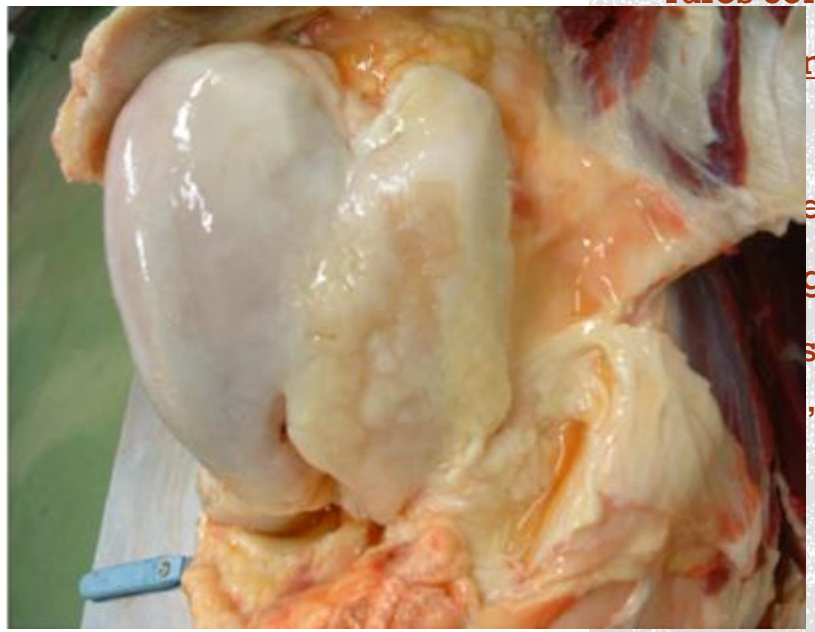
jdetilleux@ulg.ac.be

Déterminisme génétique

2/Complexe

- Polygénique et multifactoriel

Ostéochondrose



jdetilleux@ulg.ac.be

Frequentist probability

$p(E)$ = frequency of occurrence of *event* E in a hypothetical infinite ensemble, e.g., outcomes of repeated experiment

Probability quantifies *variability*

Bayesian probability

$p(H|\mathcal{P})$ = strength of an *argument* $H|\mathcal{P}$ reasoning from premises $\mathcal{P}$ to hypothetical conclusion H on $[0, 1]$ scale

Probability quantifies *uncertainty*

Déterminisme génétique

2/Complexe

- Polygénique et multifactorielle

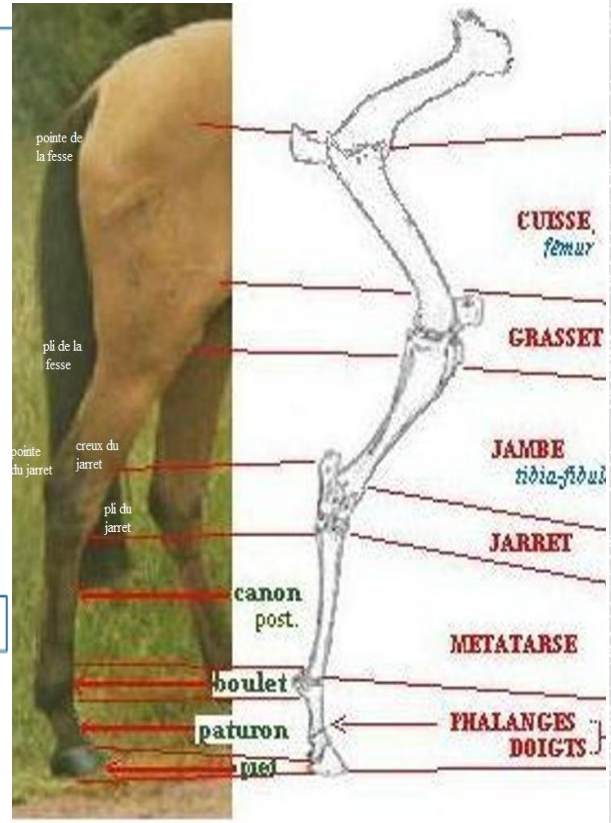
Heritability of OC (v. Grevenhof et al., 2009)

Femoropatellar (FP) OC/OCD						
Dutch WB stallions	(n=1965)	(OC)	11.5	0.09	ATM (REML, DL)	I
French WB	103 sires (n=733)	(OC)	1-7	0.00-0.17	LSM	II
Italian WB	75 sires (n=350)	(OCD)	16.6	$0.09^{0.24}$	ATM (AIREML)	III
Tarsocrural (TC) OC/OCD						
Dutch WB stallions	(n=1965)	OC	16.0	0.11	ATM (REML, DL)	I
Dutch WB mares	30 sires (n=590)	OC	13.7	$0.01^{0.06}$	LSM (REML)	IV
Dutch WB mares	30 sires (n=590)	OC	13.7	$0.14^{0.17}$	LAM (REML)	IV
French WB	103 sires (n=733)	OC	11-13	0.00-0.02	LSM	II
Hanoverian WB	165 sires (n=624)	OC	10.5	$0.06^{0.06}$	LAM (REML)	V
SB Trotters	39 sires (n=644)	OC	14.3	0.52	STM (REML)	VI
SB Trotters	24 sires (n=793)	OC	10.5	$0.27^{0.08}$	LSM	VII
Hanoverian WB	3725	OCD	9.6	$0.37^{0.04}$	LAM (REML, DL)	VIII
Hanoverian WB	569 sires (n=5,231)	OCD	9.2	$0.28^{0.04}$	LAM (REML, DL)	IX
Hanoverian WB	569 sires (n=5,231)	OCD	9.2	$0.27^{0.04}$	LSM (REML, DL)	IX
Hanoverian WB	569 sires (n=5,231)	OCD	9.2	$0.17^{0.07}$	STM (G5)	IX
Danish Trotters	9 sires (n=325)	OCD	12.0	$0.26^{0.14}$	STM	X
Metacarpophalangeal/ metatarsophalangeal (MCP/MTP) OC/OCD						
French WB	103 sires (n=733)	OC	8-11	0.04-0.21	LSM	II
Hanoverian WB	165 sires (n=624)	OC	18.3	$0.12^{0.09}$	LAM (REML	V
Hanoverian WB	(n=3,725)	OCD	20.8	$0.19^{0.03}$	LAM (REML, DL)	VIII
Hanoverian WB	569 sires (n=5,231)	OCD	23.5	$0.17^{0.03}$	LAM (REML, DL)	IX
Hanoverian WB	569 sires (n=5,231)	OCD	23.5	$0.17^{0.03}$	LSM (REML, DL)	IX
Hanoverian WB	569 sires (n=5,231)	OCD	23.5	$0.12^{0.03}$	STM (G5)	IX
SB Trotters	39 sires (n=644)	OCD	17.7	0.21	STM (REML)	VI
SB Trotters	24 sires (n=793)	OCD	21.5	$0.17^{0.06}$	LSM	VII
ALL joints (FP+TC+MCP/MTP)						
Italian WB	75 sires (n=350)	OCD	16.6	$0.14^{0.23}$	LAM (REML, DL)	III

stifle: 0 - 0.17

hock: 0.0 - 0.52

fetlock: 0.04 - 0.21



CONSEIL GÉNÉTIQUE

Définition

Tares connues

Déterminisme

- Simple
- Complexe

Conseil génétique

- Risques
- Plans d'élevage

WAGENINGEN UNIVERSITY
WAGENINGEN UR

jdetilleux@ulg.ac.be

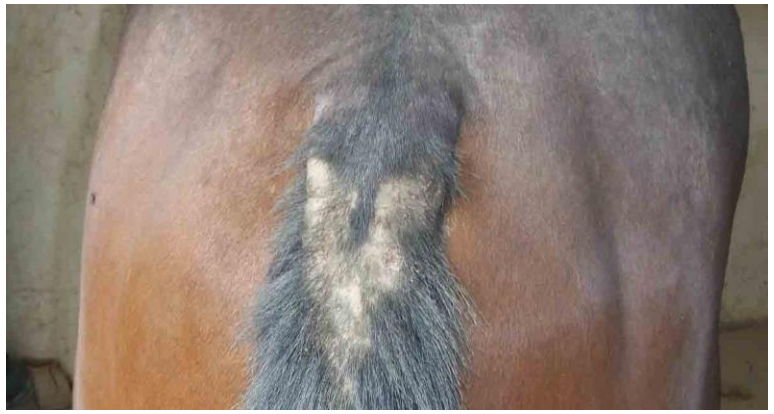
Déterminisme génétique

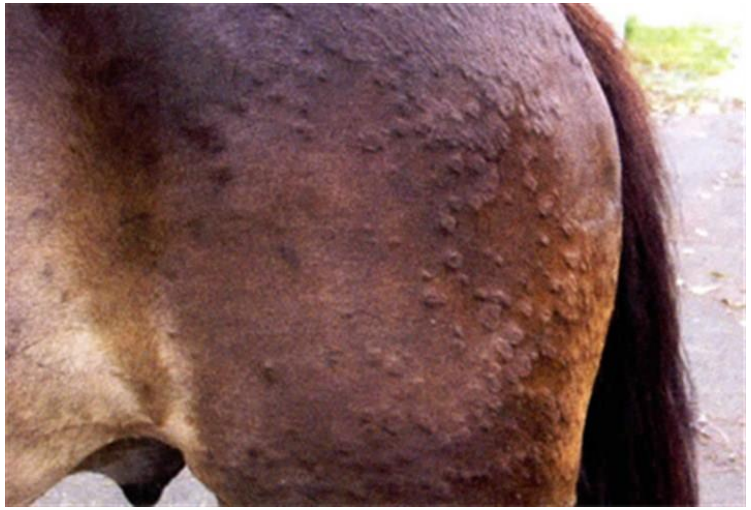
2/Complexe

- Polygénique et multifactorielle

EX. Dermite estivale – hypersensibilité aux piqures d'insectes

Génétique X Environnement





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