

Pros and cons of hitchhiking: The truth about inbreeding in dairy cattle

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Topics for discussion

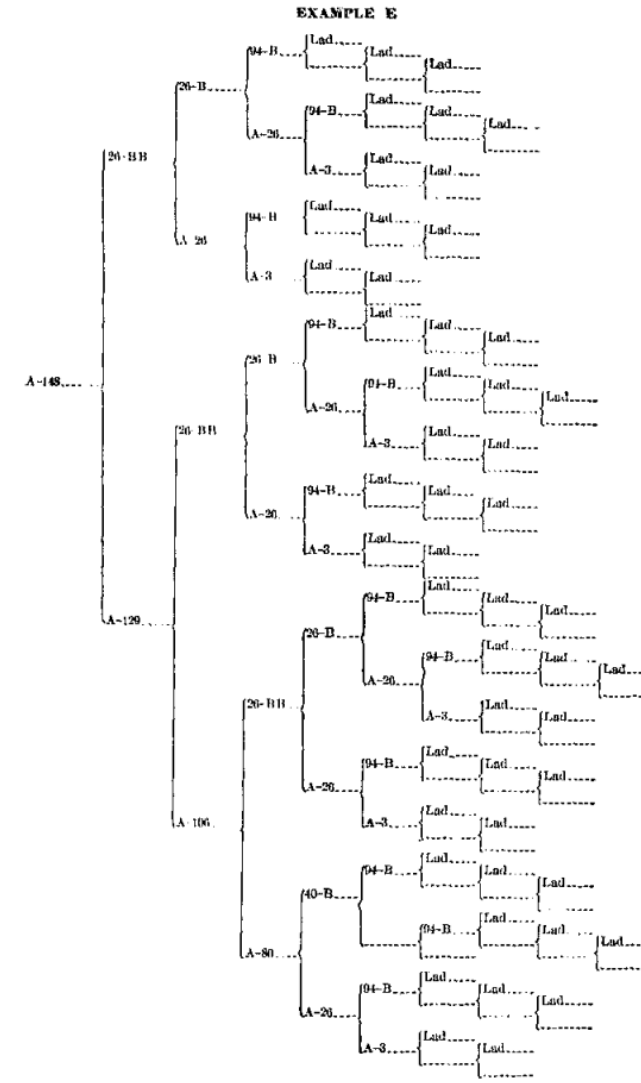
- **What is inbreeding, and what causes it?**
- **(Why) is it bad?**
- **How do we measure it?**
- **Is it changing in the Holstein breed?**
- **Can we do anything about it?**
- **Take-home messages**



What is inbreeding, and what causes it?

Inbreeding results from the mating of related animals

- It's the proportion of the genome that is **identical** because it came from the same ancestor
- Inbreeding results when **related** animals are mated to one another
- Inbreeding is **inevitable** in a finite population
 - It can be managed, but not stopped



Cow A-148
 $f_p = 0.646$

Source: Swett et al. (1949)

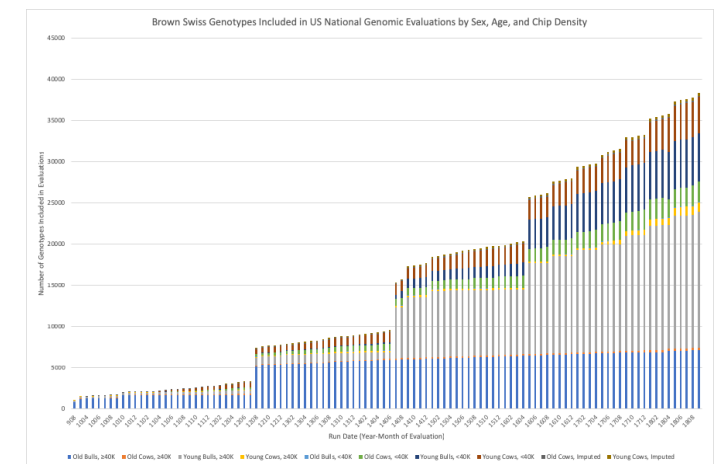
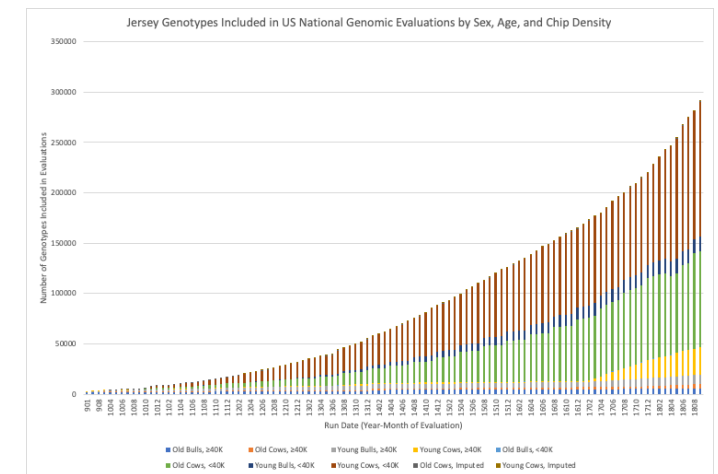
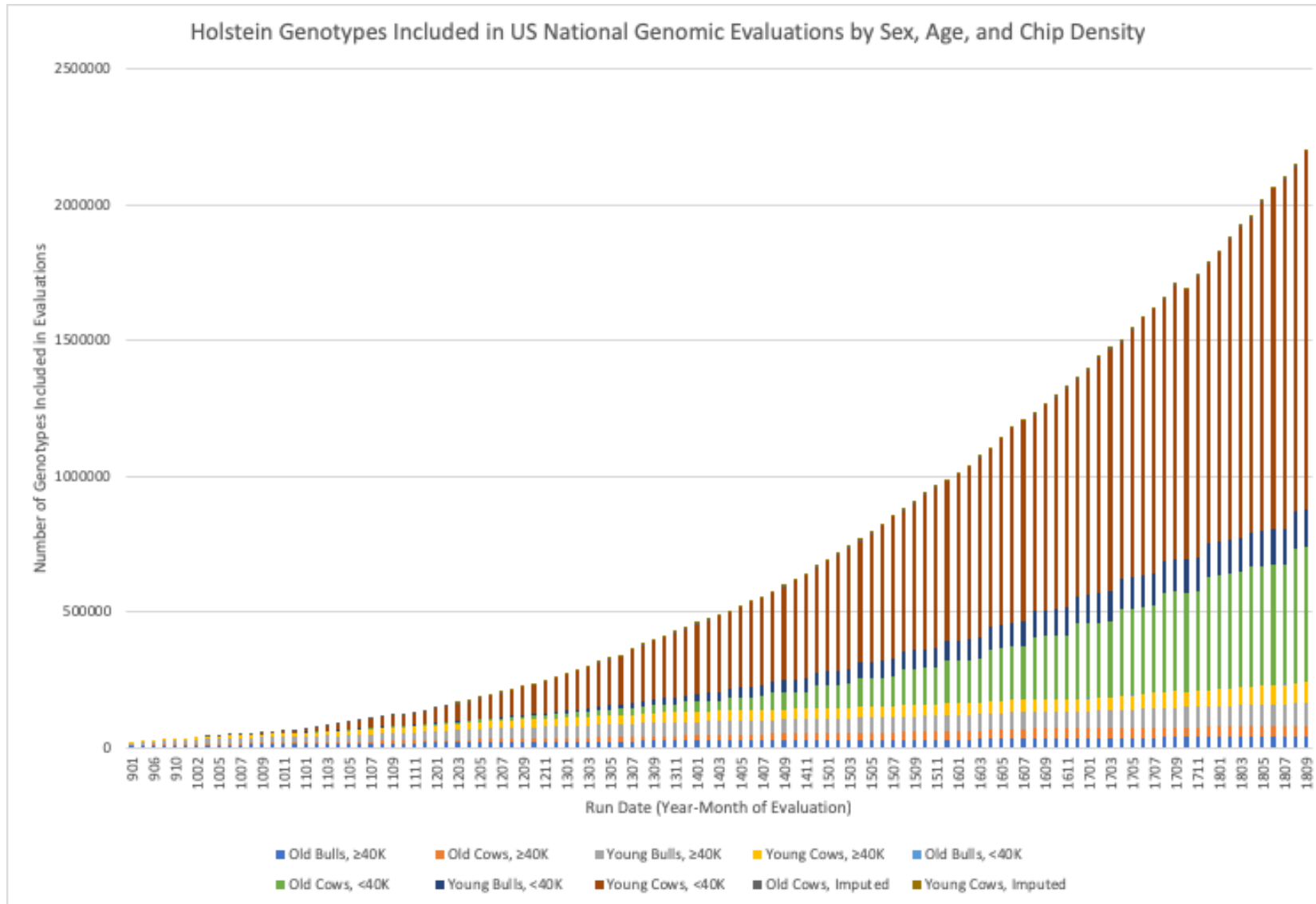
More efficient selection, more inbreeding

Theory	Author	Year	Species
Single-gene inheritance	Mendel	1865	Peas
Multiple-gene inheritance	Fisher	1918	Humans
Pedigree relationship matrix	Wright	1922	Cattle
Selection index	Hazel & Lush	1943	Plants, cattle
Mixed linear models	Henderson	1963	Cattle
Genomic prediction	Meuwissen	2001	Animals
Genomic relationship matrix	VanRaden	2008	Cattle

Also application

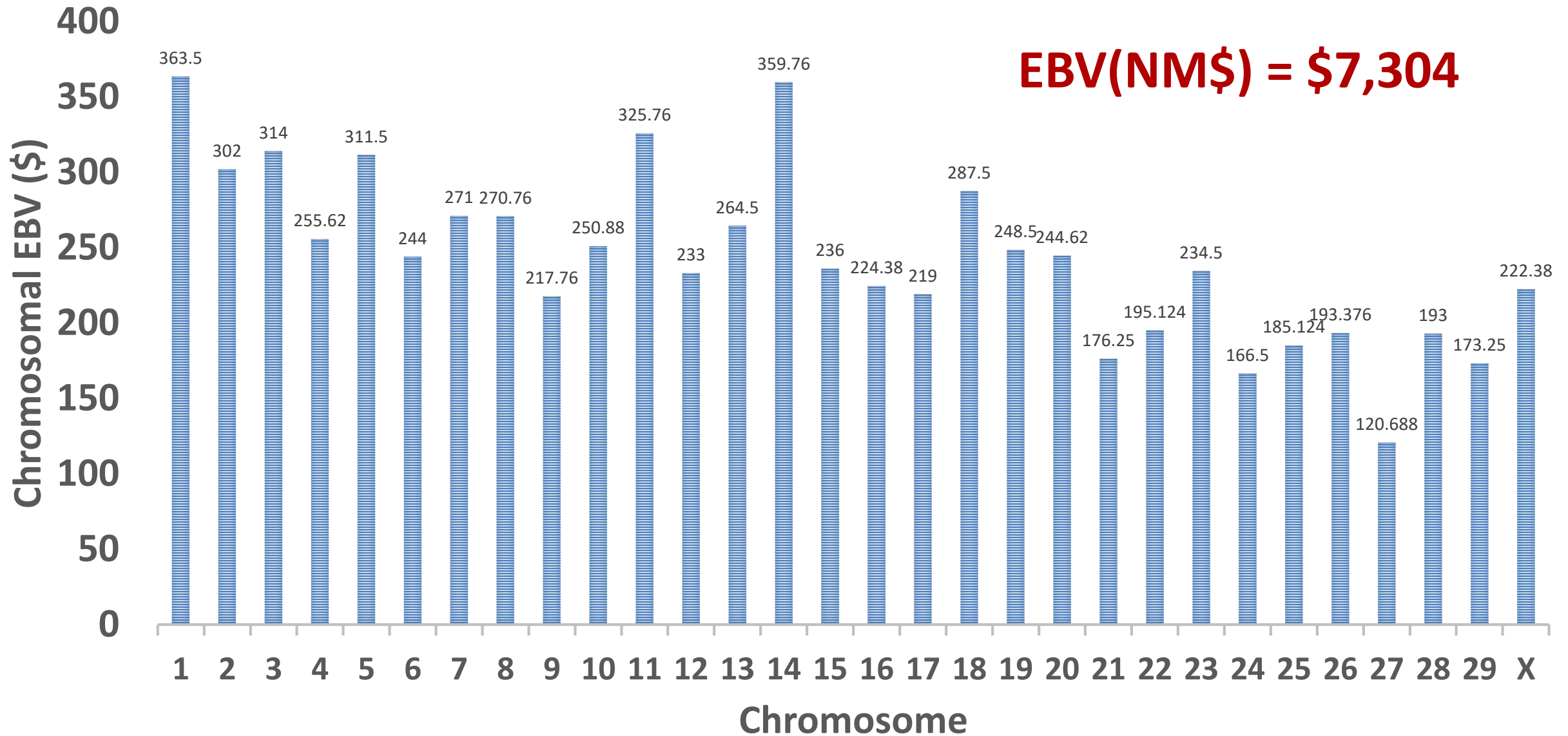
**First database with 1 million genotyped individuals was
USDA/Council on Dairy Cattle Breeding in July 2015**

Genotypes are plentiful



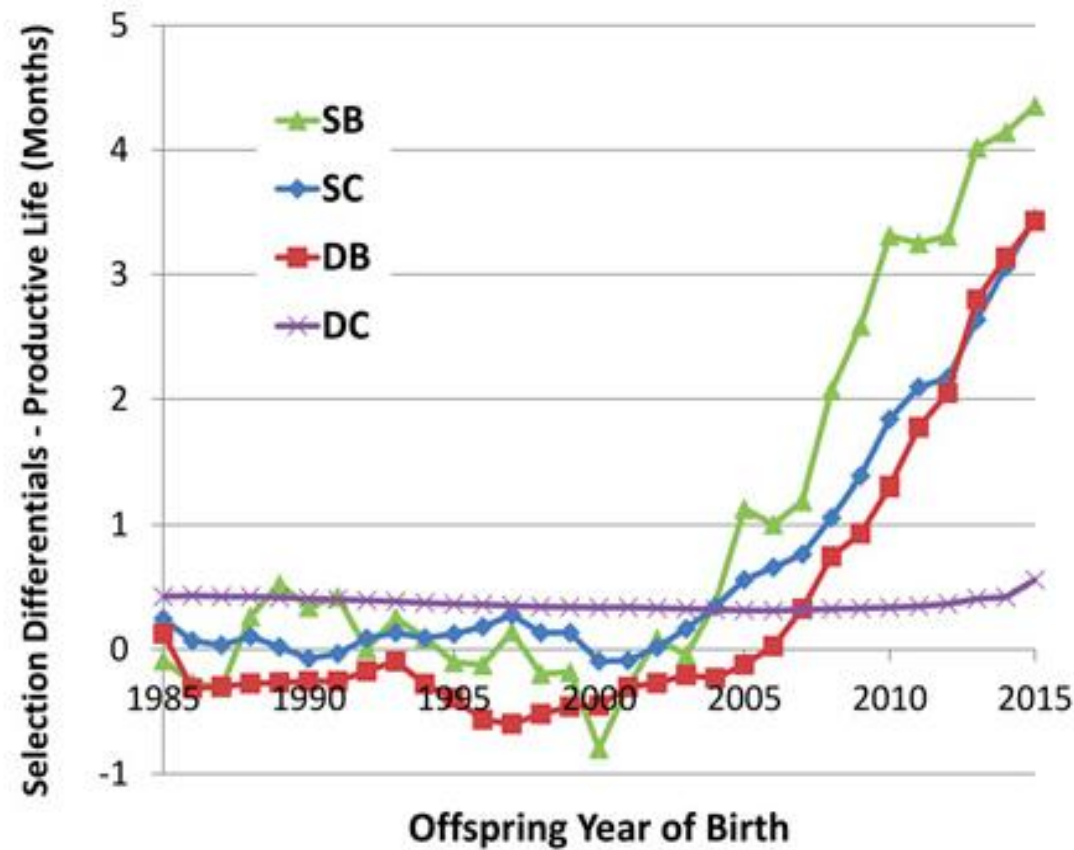
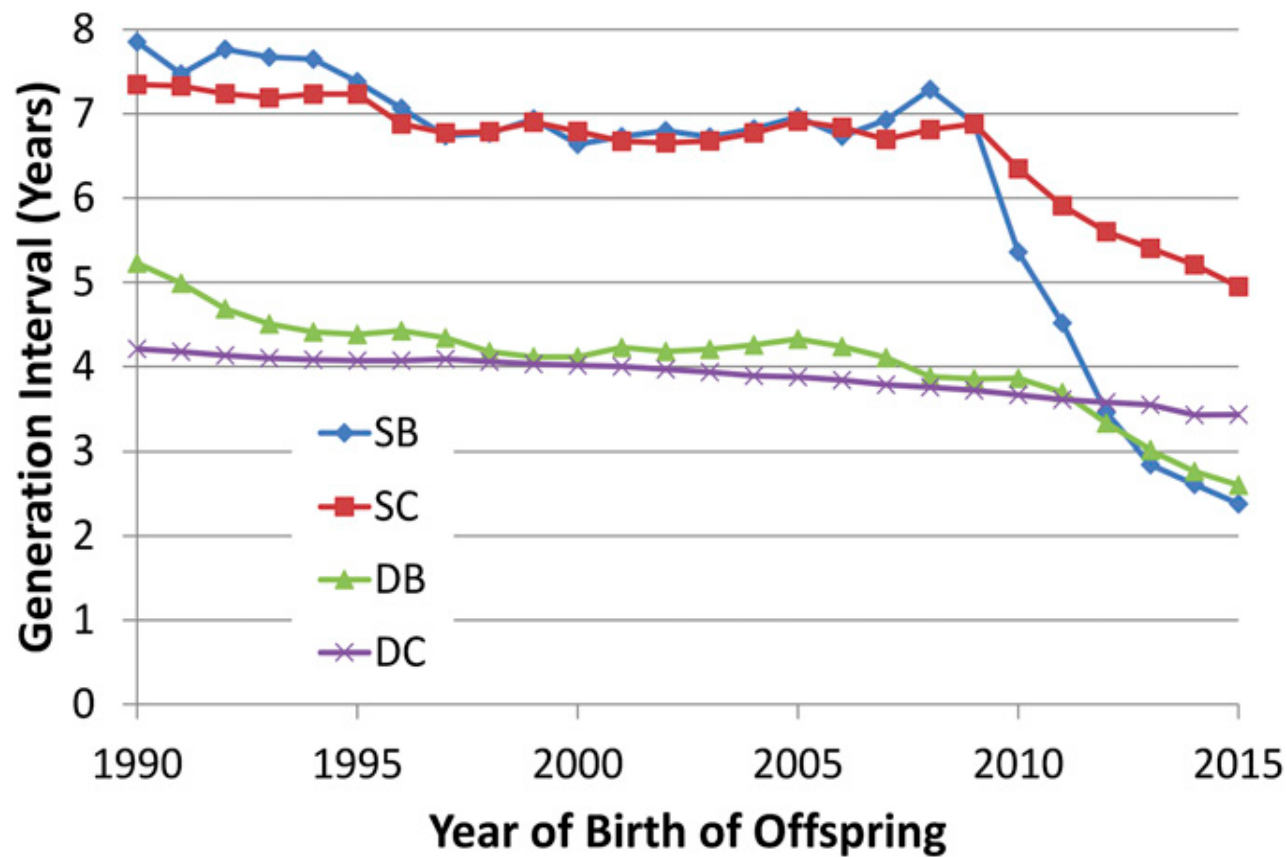
Source: Council on Dairy Cattle Breeding (2019).

We want to get the best DNA together in one animal



After Cole and VanRaden (2011). **USDA**

Genomic selection lets us go really fast



Source: García-Ruiz et al. (2016).

We're in an endless race to find the highest index bull

INDUSTRY:

- AI breeds bulls to meet **market demands**
- High genetic merit bulls have **high marketability**
- Lower inbreeding rates result in **slower genetic gains**
- Who is willing to go slower to better manage inbreeding?



Source: Wikimedia Commons.

(Why) is it bad?

Inbreeding often has undesirable effects

- **Harmful loci increase in frequency and are more likely to be paired-up**
 - e.g., Haplotypes such as HH1
 - This is thought to account for most inbreeding depression
- **Slow inbreeding more effective at selecting against harmful loci**
- **Undesirable loci travel along with desirable loci if they're close together ("hitchhiking")**

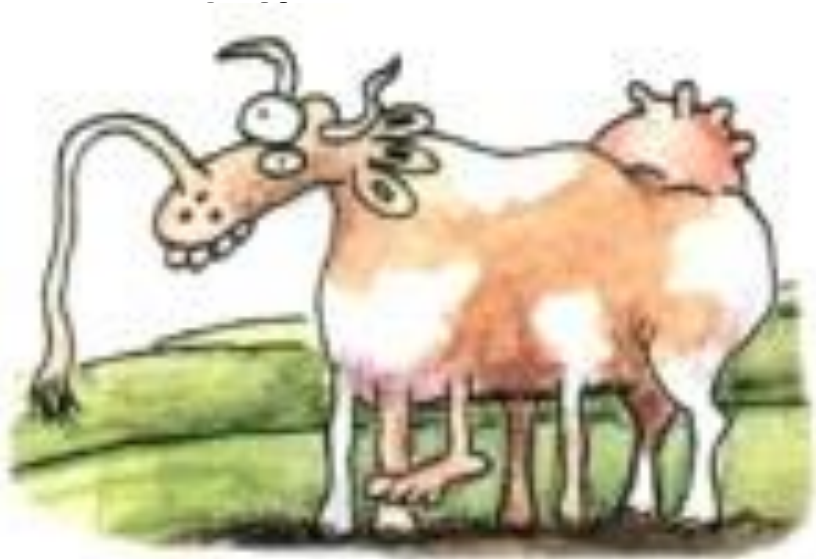


Trait	Effect/1% gain
Milk yield	-50 lb
Fat yield	-1.5 lb
Birth weight	-0.24 lb
Yearling weight	-1.5 lb
Weight at 4 years	-5.0 lb
Height	Slight decrease
Survival to 1 st calf	-2 %
Services to conception	+0.05
Days to first service	+3.0
Age at puberty	Delayed

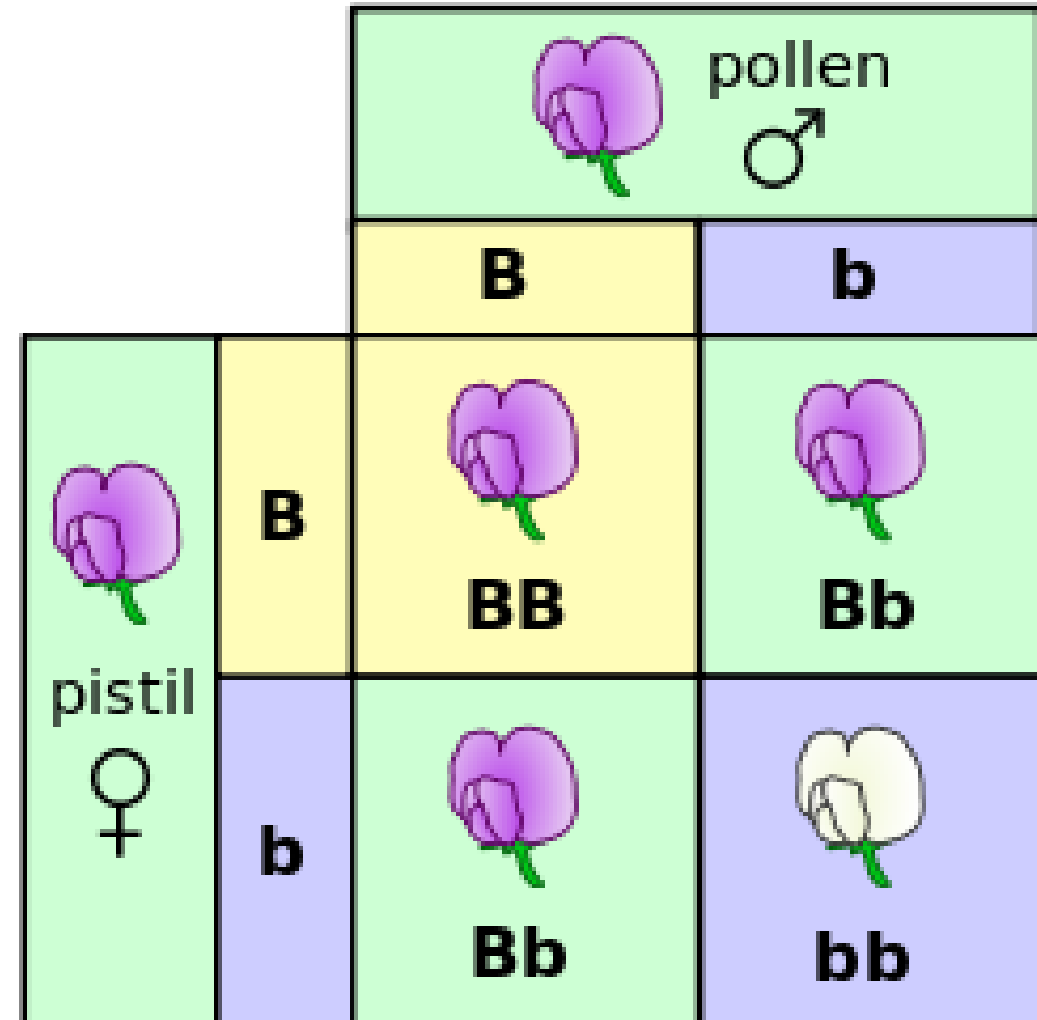
Source: Schmidt et al. (1988).

Mendelian recessives are exposed by inbreeding

- Classical model of inheritance
- One locus, typically with two alleles
- Often exhibit complete dominance
- e.g



Source: The Far Side.



Source: Wikimedia.

Mendel's garden: a pilgrimage



Source: Author.

There are many known recessives in U.S. Holsteins

Haplotype	Functional/ <i>Gene</i> name	Chromosome	Location (Mbp)	Haplotype frequency (%)	Timing ¹
HBR	Black/red coat color/ <i>MC1R</i> (<i>MSHR</i>)	18	14.71	0.75	—
HCD	Cholesterol deficiency/ <i>APOB</i>	11	77.87	2.28	W
HDR	Dominant red color/ <i>MC1R</i> (<i>MSHR</i>)	3	9.36	0.03	—
HH0	Brachyspina/ <i>FANCI</i>	21	20.77	1.65	E,B
HH1	<i>APAF1</i>	5	62.81	1.28	E
HH2	—	1	93.50-95.58	1.21	E
HH3	<i>SMC2</i>	8	93.75	2.64	E
HH4	<i>GART</i>	1	1.99	0.23	E
HH5	<i>TFB1M</i>	9	91.85-91.94	2.39	E
HH6	<i>SDE2</i>	16	29.01-29.05	0.44	Old age
HHB	<i>BLAD/ITGB2</i>	1	144.77	0.21	W
HHC	<i>CVM/SLC35A3</i>	3	43.26	1.10	E,B
HHD	<i>DUMPS/UMPS</i>	1	69.15	0.01	E
HHM	Mulefoot/ <i>LRP4</i>	15	76.81	0.05	B
HHP	Polledness (dominant)/ <i>POLLED</i>	1	2.57	0.88	—
HHR	Red coat color/ <i>MC1R</i> (<i>MSHR</i>)	18	14.71	3.29	—

¹Timing of embryonic loss/calf death for homozygous animals: B = calf death at/shortly after birth, E = embryonic loss/abortion, W = calf death weeks/months after birth (Cole et al., 2016; Cole et al., 2018).

Is the number of defects increasing?

- **MacArthur et al. (2012)** estimated that human genomes contain **~100** loss-of-function mutations, and **~20** completely inactivated genes
- The mutations are there even if we have not identified them yet
 - Example: HH6, mutation in *SDE2* (**Fritz et al., 2018**)
- Our **detection methods are improving** as our technology improves
- New mutations do occur, but they are very rare

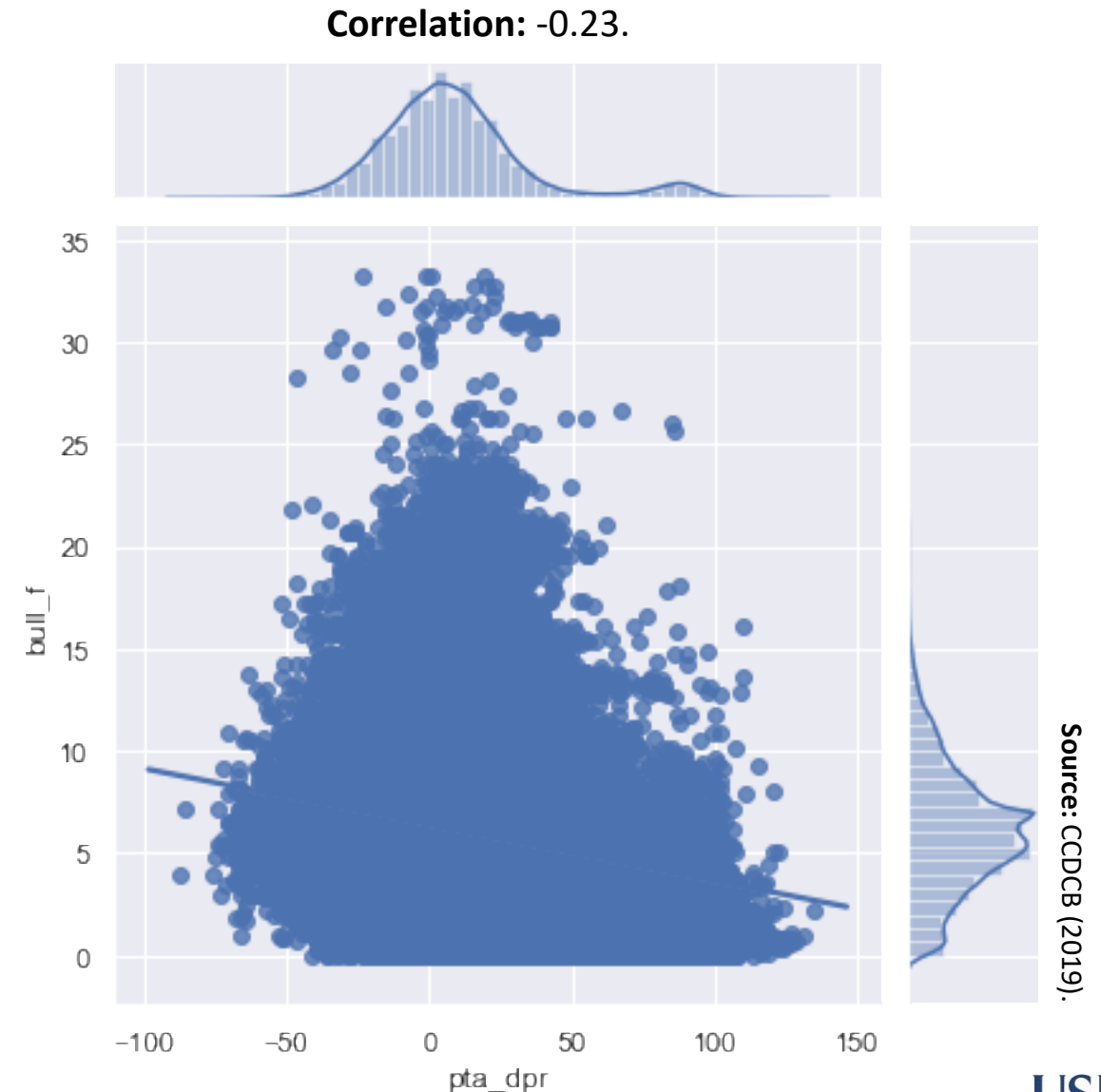
Estimated cost of genetic load

- **Cole et al. (2016)** estimated annual losses of at least **\$10.7** million due to known recessives.
- Average losses were **\$5.77**, **\$3.65**, **\$0.94**, and **\$2.96** in Ayrshire, Brown Swiss, Holstein, and Jersey, respectively.
- This is the economic impact of genetic load as it affects fertility and perinatal mortality.
- Actual losses are likely to be higher.

We don't really know how much is too much

- Selection is now on indices that **include** health and fitness data
- This avoids past mistakes from focusing on only **one or a few** traits
- Will we see genetic merit gradually fade away, or will we cross a threshold and suddenly crash?
- **Interviewer:** “How did you go bankrupt?”

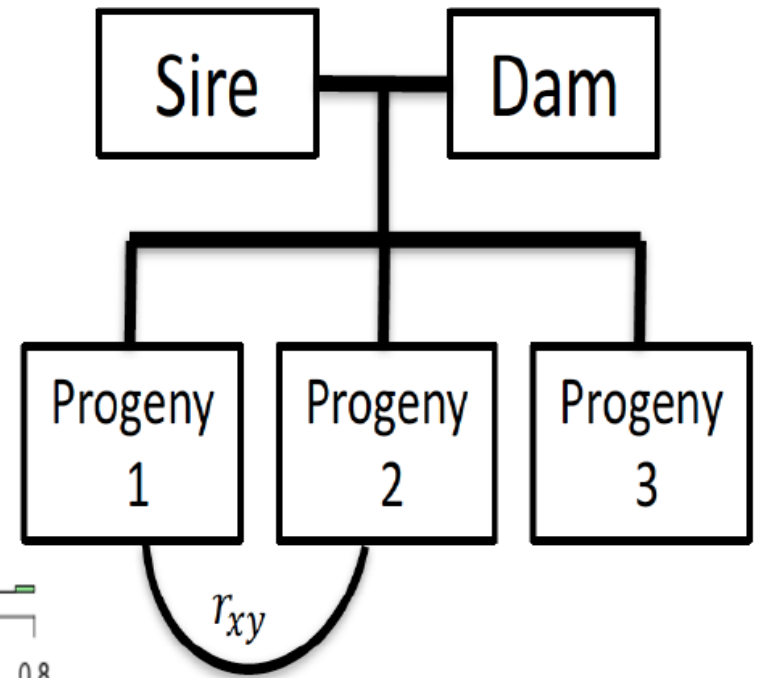
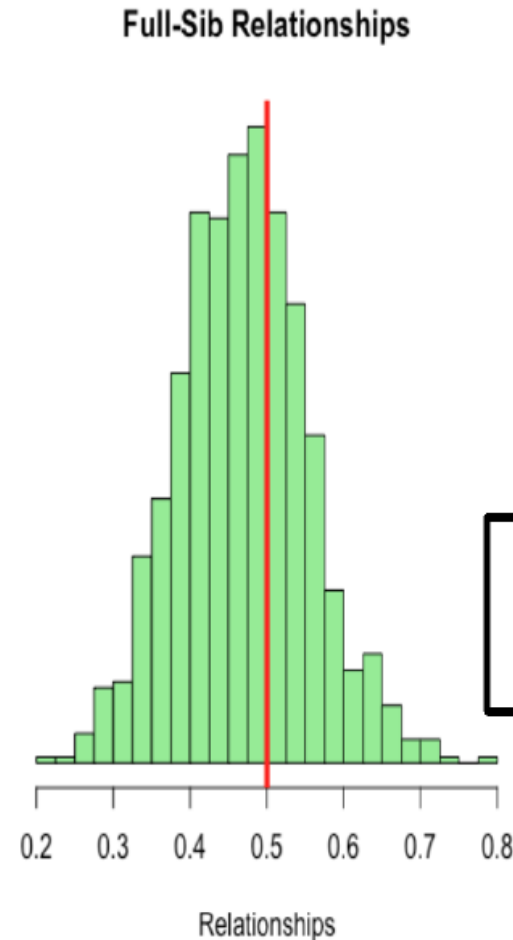
Ernest Hemingway: “Two ways. Gradually, then suddenly.”



How do we measure it?

Pedigree and genomic inbreeding

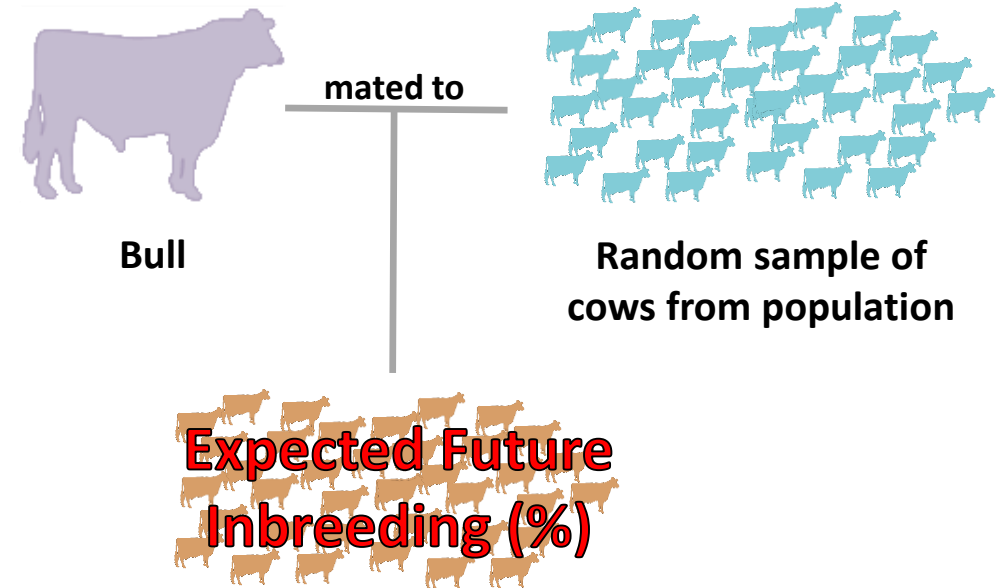
- **Pedigree inbreeding** is based on the passing of chromosomes from parents to offspring over many generations
- **Genomic inbreeding** is based on the actual pieces of chromosomes passed from parents to offspring over many generations
- Inbreeding **increases** as pedigrees get deeper
- However, the **age** of inbreeding may matter, too



Source: Christian Maltecca (2019).

Expected future inbreeding (EFI)

- Inbreeding is a property of an **individual** animal
- Expected future inbreeding is the **average** inbreeding expected when a bull is mated to a random sample of cows from the population
- The more related a bull is to the population, the **higher** the EFI
- Genomic future inbreeding (GFI) is based on the same concept



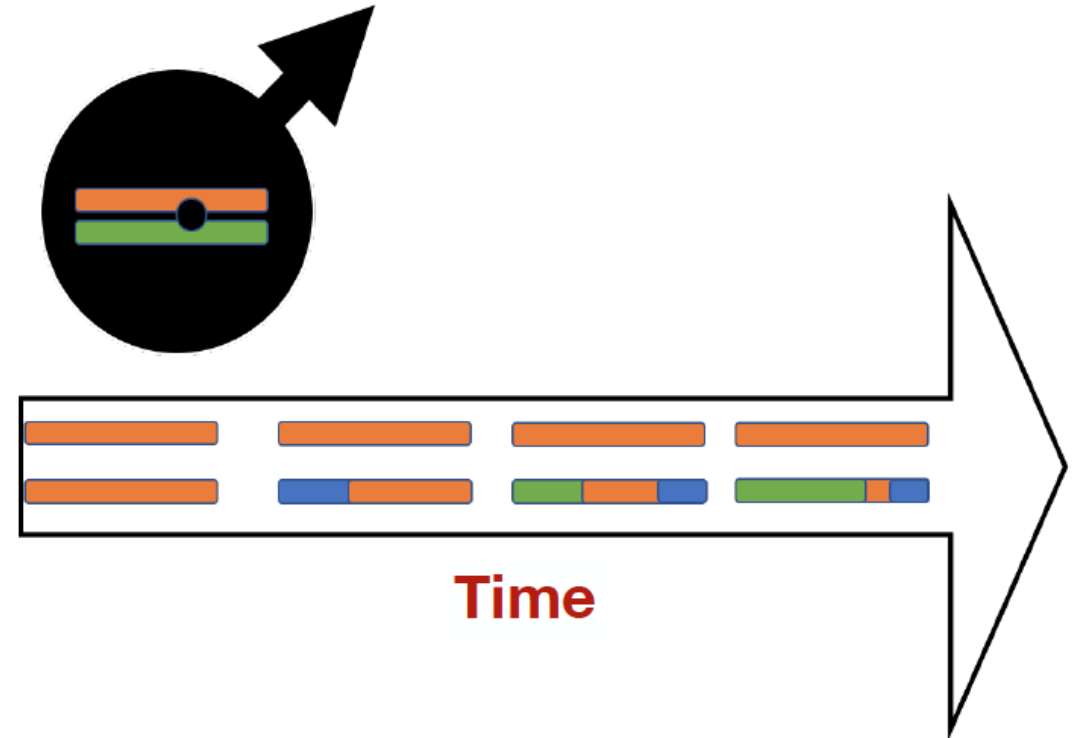
7H06417 O MAN 

O-BEE MANFRED JUSTICE-ET (EX-94-GM)
HOUSA122358313 100% RHA-NA
TR TV TL TD
Born: 03/08/1998
aAa: 435216 DMS: 345,456
Breeder: Gary, Gaylon & Steve Obert, Dakota, IL
Beta-Casein: A1A2 GFI: 10.4%
Kappa-Casein: BB Beta-Lactoglobulin: AB
Haplotypes HH3C HH1T HH2T HH4T HH5T HH6T

Source: Select Sires.

Runs of homozygosity (ROH)

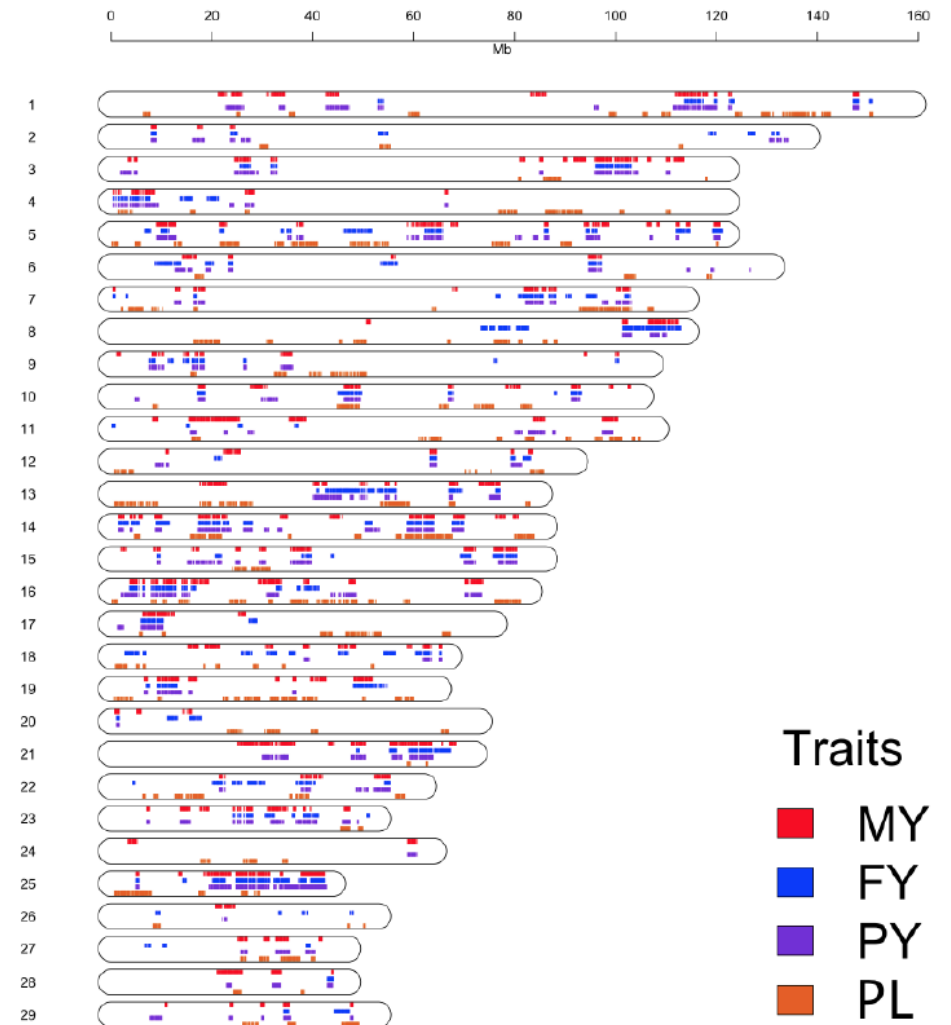
- **Recent** inbreeding produces long stretches of DNA shared in common
- **Old** inbreeding is represented by much shorter pieces of shared DNA
- ROH provide information about **specific places** in the genome
- Old stretches of inbreeding may have been **purged** of harmful loci



Source: Christian Maltecca (2019).

ROH used to find undesirable, but not lethal, regions

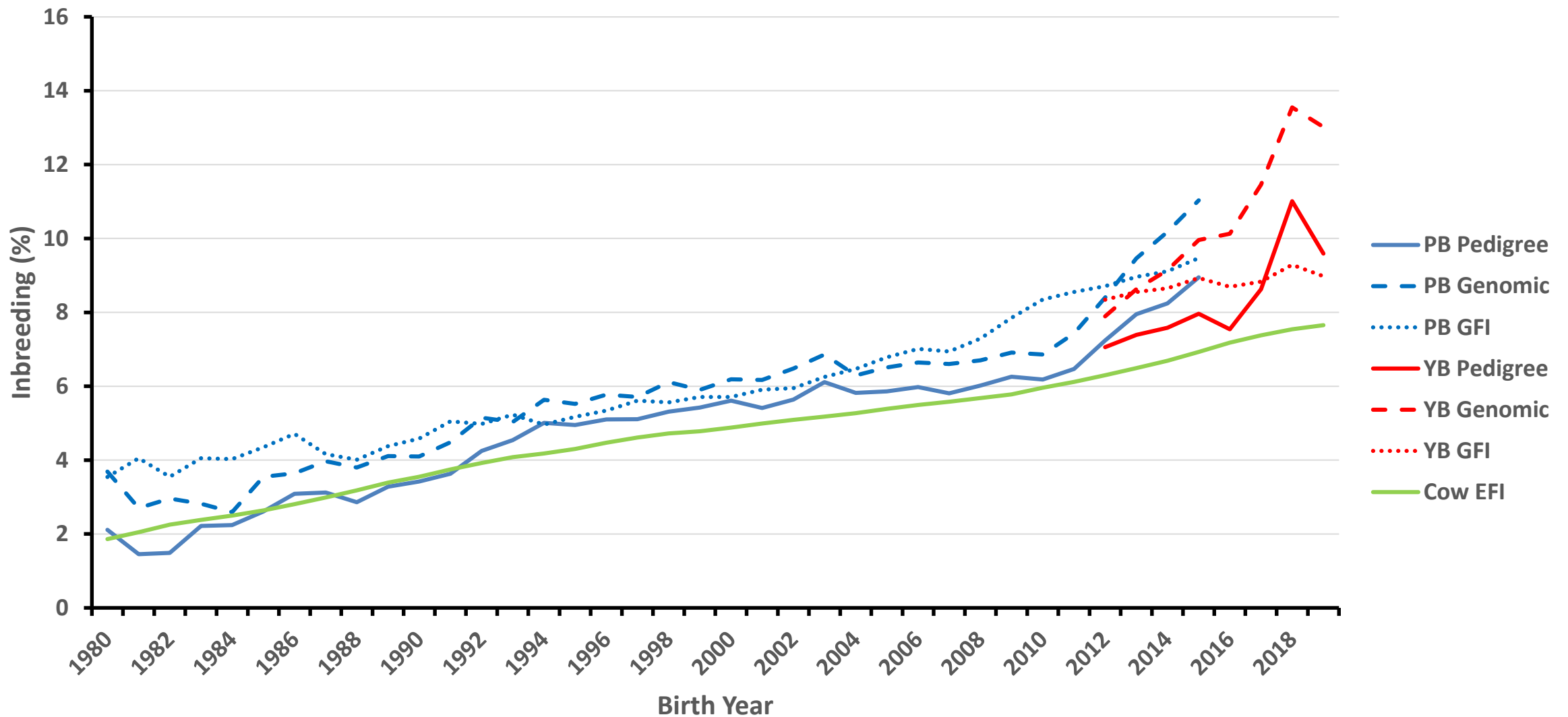
- Some mutations in the population are **sub-lethal**: they harm performance but don't kill animals
- They are more difficult to find than lethal haplotypes
- May appear in ROH



Source: Christian Maltecca (2019).

Is it changing in the Holstein breed?

Pedigree and genomic inbreeding of Holsteins



Source: CDCB (April 2019) 

ROUND OAK RAG APPLE ELEVATION (007H000058)

f_p	0.0
f_G	-3.3
NM\$	-567
TPI	843

	HOUSA000000933122	1944-03-28	WIS IDEAL		
	HOUSA000001013415	1947-03-28	Wis Burke		
	HOUSA000002454577	1944-03-28			
HOUSA000001271810	HOUSA000000933122	1944-03-28	WIS IDEAL		
	HOUSA000001013415	1947-03-28	Wis Burke		
	HOUSA000002454577	1944-03-28			
HOUSA000003348181	HOUSA000000933122	1944-03-28	WIS IDEAL		
	HOUSA000001013415	1947-03-28	Wis Burke		
	HOUSA000002454577	1944-03-28			
	HOUSA000003348181	1950-09-18	CARINE MERCEDES BURKE IDEAL		
	HOUSA000002948518	1947-09-19			
HOUSA000001491007	HOUSA000000933122	1944-03-28	WIS IDEAL		
	HOUSA000001013415	1947-03-28	Wis Burke		
	HOUSA000002454577	1944-03-28			
	HOUSA000003348181	1950-09-18	CARINE MERCEDES BURKE IDEAL		
	HOUSA000002948518	1947-09-19			
	HOUSA000001491007	1965-08-30	ROUND OAK RAG APPLE ELEVATION	4	778k
	HOUSA000000848777	1947-01-04	OSBORNDALE TY VIC		
	HOUSA000001189870	1952-04-26	OSBORNDALE IVANHOE	1	58k
	HOUSA000002471271	1947-11-29			
HOUSA000005749758	HOUSA000000933122	1944-03-28	WIS IDEAL		
	HOUSA000001013415	1947-03-28	Wis Burke		
	HOUSA000002454577	1944-03-28			
	HOUSA000003348181	1950-09-18	CARINE MERCEDES BURKE IDEAL		
	HOUSA000002948518	1947-09-19			
	HOUSA000001491007	1965-08-30	ROUND OAK RAG APPLE ELEVATION	4	778k
	HOUSA000000848777	1947-01-04	OSBORNDALE TY VIC		
	HOUSA000001189870	1952-04-26	OSBORNDALE IVANHOE	1	58k
	HOUSA000002471271	1947-11-29			
	HOUSA000005749758	1962-07-14	ROUND OAK IVANHOE EVE		
	HOCAN000000239301	1951-11-30	ROSAFE CENTURION		
	HOUSA000001294924	1954-02-15	GLENAFTON GAIETY		
	HO-----				
HOUSA000004855614	HOUSA000000933122	1944-03-28	WIS IDEAL		
	HOUSA000001013415	1947-03-28	Wis Burke		
	HOUSA000002454577	1944-03-28			
	HOUSA000003348181	1950-09-18	CARINE MERCEDES BURKE IDEAL		
	HOUSA000002948518	1947-09-19			
	HOUSA000001491007	1965-08-30	ROUND OAK RAG APPLE ELEVATION	4	778k
	HOUSA000000848777	1947-01-04	OSBORNDALE TY VIC		
	HOUSA000001189870	1952-04-26	OSBORNDALE IVANHOE	1	58k
	HOUSA000002471271	1947-11-29			
	HOUSA000005749758	1962-07-14	ROUND OAK IVANHOE EVE		
	HOCAN000000239301	1951-11-30	ROSAFE CENTURION		
	HOUSA000001294924	1954-02-15	GLENAFTON GAIETY		
	HO-----				
	HOUSA000004855614	1959-01-07			
	HOUSA000001064446	1947-09-23	ROUND OAK MONTVIC P F GENERAL		
	HOUSA000003757944	1953-11-16			
	HOUSA000002292061	1949-02-17			



MARA-THON BW MARSHALL-ET (007H005375)

f_p	5.8
f_G	8.9
NM\$	-78
TPI	1548

		HOUSA000001556373	1968-11-19	GLENDELL ARLINDA CHIEF	4	778k
		HOUSA000001697572	1975-11-20	ARLINDA ROTATE	4	778k
		HOUSA000007370146	1969-08-14			
	HOUSA000001879149		1982-03-06	ARLINDA MELWOOD-ET	4	778k
		HOUSA000001531866	1968-01-27	PACLAMAR COMBINATION		
		HOUSA000009311697	1976-12-10	ARLINDA COMBI MELODY		
		HOUSA000008155956	1972-05-04	ARLINDA CARLIN MELODY		
	HOUSA000002103297		1989-05-19	MAIZEFIELD BELLWOOD-ET	1	58k
		HOUSA000001441440	1963-01-20	PENSTATE IVANHOE STAR	1	58k
		HOUSA000001667366	1974-05-16	CARLIN-M IVANHOE BELL	4	778k
		HOUSA000007832117	1970-10-18	B & W HEILO CREAMELLE		
	HOUSA000012052401		1984-10-13	BREN-WAY BELL BETSY		
		HOUSA000001626813	1972-08-06	MARSHFIELD ELEVATION TONY	1	58k
		HOUSA000011302033	1982-09-15	BREN-WAY TONY BESSIE		
		HOUSA000010533152	1980-07-01			
	HOUSA000002290977		1995-03-24	MARA-THON BW MARSHALL-ET	4	778k
		HOUSA000001441440	1963-01-20	PENSTATE IVANHOE STAR	1	58k
		HOUSA000001667366	1974-05-16	CARLIN-M IVANHOE BELL	4	778k
		HOUSA000007832117	1970-10-18	B & W HEILO CREAMELLE		
	HOUSA000001912270		1983-01-25	EMPRISE BELL ELTON	4	778k
		HOUSA000001556373	1968-11-19	GLENDELL ARLINDA CHIEF	4	778k
		HOUSA000010248397	1979-06-02	MONARCHIAL GLENDELL EFFIE		
		HOUSA000008786528	1974-07-23			
	HOUSA000014840387		1990-05-02	MORGAN-VALLEY ELTON MARA		
		HOUSA000001650414	1973-06-28	S-W-D VALIANT	4	778k
		HOUSA000001818972	1980-02-02	MEL-EST VALIANT IROS MELVIN	1	58k
		HOUSA000008560247	1973-11-02	MEL-EST ELEVATION IROSE ROSITA		
	HOUSA000012936456		1986-05-26	MORGAN-VALLEY MARCIS MARY		
		HOUSA000001682467	1975-01-22	WAGNERSCREST IVANHOE ASTRONAUT	1	58k
		HOUSA000011021502	1982-03-01			
		HOUSA000008510667	1973-08-09			

PINE-TREE ACURA-ET (029HO18960)

f_p	12.8
f_G	17.1
NM\$	1,065
TPI	2,895

	HOUSA000139005002	2007-09-17	COYNE-FARMS DORCY-ET	1	58k
	HO840003006972816	2010-06-22	MOUNTFIELD SSI DCY MOGUL-ET	1	58k
	HOUSA000062784081	2006-04-23	MOUNTFIELD MARSH MAXINE-ET	1	58k
HOUSA000072254526		2013-01-05	WOODCREST MOGUL YODER-ET	8	77k
	HOUSA000060597003	2003-03-03	ENSENADA TABOO PLANET-ET	4	778k
	HO840003008363689	2011-03-21	WOODCREST PLANET YAKARA-ET	3	3k
	HOUSA000066893887	2009-05-18	COYNE-FARMS BKEYE YVONNE-ET	1	58k
HO840003128557482		2015-11-15	ABS ACHIEVER-ET	17	140k
	HOUSA000060996956	2004-10-31	BADGER-BLUFF FANNY FREDDIE	1	58k
	HONLD000543756297	2011-06-16	APINA ALTAEMBASSY-ET	2	58k
	HOUSA000064969166	2008-12-01	STRAUSSDALE PLANET ELLA	1	58k
HO840003013177242		2013-09-30	COMPASS-TRT AMRC AE J925-ET	8	77k
	HOUSA000064966739	2008-12-23	ROYLANE SOCRA ROBUST-ET	1	58k
	HOUSA000070640281	2011-07-26	SEAGULL-BAY MISS AMERICA-ET	2	58k
	HOUSA000066228178	2009-04-16	AMMON-PEACHEY SHAUNA-ET	1	58k
HO840003142332520		2017-11-25	PINE-TREE ACURA-ET	17	140k
	HOUSA000069398748	2010-06-30	MOUNTFIELD MSY MAURICE-ET	2	58k
	HO840003009554583	2012-05-22	S-S-I MAURICE PARTYROCK-ET	2	58k
	HO840003006972817	2010-06-22	JK-GOLD SSI DORCYP7042-ET	1	58k
HO840003014334961		2014-01-01	S-S-I PARTYROCK PROFIT-ET	8	77k
	HO840003006972816	2010-06-22	MOUNTFIELD SSI DCY MOGUL-ET	1	58k
	HO840003009554577	2012-05-17	S-S-I MOGUL MAHO 8054-ET	7	9k
	HO840003004672693	2010-08-26	S-S-I ROBUST MAHO 7083-ET	2	58k
HO840003132116871		2016-03-13	PINE-TREE 9882 PROF 7019-ET	20	19k
	HOUSA000064966739	2008-12-23	ROYLANE SOCRA ROBUST-ET	1	58k
	HOUSA000069981349	2010-12-28	SEAGULL-BAY SUPERSIRE-ET	2	58k
	HOUSA000066228178	2009-04-16	AMMON-PEACHEY SHAUNA-ET	1	58k
HO840003011890130		2013-12-02	OCD SUPERSIRE 9882-ET	17	140k
	HOUSA000064966739	2008-12-23	ROYLANE SOCRA ROBUST-ET	1	58k
	HO840003008315320	2011-03-08	OCD ROBUST SHIMMER-ET	2	58k
	HOUSA000066228180	2009-04-18	AMMON-PEACHEY SHANA-ET	1	58k

Can we do anything about it?

Scientists are trying to understand what's been lost

- Almost all Y chromosomes in the Holstein bull population are from **Elevation** and **Chief**
- It's unclear what might have been **lost** along the way
- A small genetic base may translate to a **fragile** population that can't respond well to changes

The screenshot shows the top of a Scientific American article. At the top left is a blue 'Subscribe' button. The 'SCIENTIFIC AMERICAN' logo is in the top right, next to a 'Cart 0' and 'Sign In | Stay Informed' link. Below the logo is a navigation bar with links for 'THE SCIENCES', 'MIND', 'HEALTH', 'TECH', 'SUSTAINABILITY', 'EDUCATION', 'VIDEO', 'PODCASTS', 'BLOGS', and 'PUBLICATIONS'. The article title 'From Two Bulls, Nine Million Dairy Cows' is prominently displayed in a large, bold font. Above the title is the 'UNDARK BIOLOGY' logo. Below the title is a sub-headline: 'Just two Y chromosomes exist in a huge population of U.S. Holsteins; researchers want to know what's been lost'. The author's name 'By Maur...' and the date '20.2019' are partially visible. A large grey audio player icon is overlaid on the text. To the left of the main image is a social media sharing grid with icons for Facebook, Twitter, LinkedIn, Email, and Print. To the right is a 'READ THIS NEXT' section with a small image and the text 'Rise of the Ag-Bots Will Not Sow Seeds of Unemployment'. The main image shows a close-up of a cow's head in a barn.

Source: O'Hagan (2019), *Scientific American*, 20 June 2019.

AI companies were trying to identify new bloodlines



Table 1

Global and North American (NA) sire numbers, before and after genomics

Birth years		Pre-genomics		Post-genomics	
		2002-2008		Bulls entered AI	All genotyped bulls
				2011	
No. of young bulls	Global	5,300	3,290	28,440	
	NA	1,660	1,335	10,685	
No. of sires of young bulls	Global	380	410	1,240	
	NA	105	155	450	
No. of most popular sires representing 50% of young bulls	Global	15	18	32	
	NA	8	9	16	
Average number of sons per sire	Global	14	8	23	
	NA	15	9	24	

Source: Miglior and Beavers, *Progressive Dairyman*, 18 July 2014.

There are many theoretically satisfying ideas...

- ...but nobody uses them
- **Geneticists don't breed cows, farmers do**
- **Many cows now mated at random to a portfolio of bulls**
- **Everyone thinks their neighbor should use different bulls**

Some methods for avoiding inbreeding

Optimal contribution theory

Minimization of progeny inbreeding

Linear programming

Look-ahead mate selection

Selection against lethal alleles

Index selection including Mendelian sampling variance

Genomic selection including dominance

U.S. PTAs are adjusted for inbreeding

Trait	Inbreeding depression/1%	Trait value in NM\$	\$ Value /1% F
Milk	-63.9	-0.004	0.3
Fat	-2.37	3.56	-8.4
Protein	-1.89	3.81	-7.2
Productive life	-0.26	21	-5.5
Somatic cell score	0.004	-117	-0.5
Daughter pregnancy rate	-0.13	11	-1.4
Cow conception rate	-0.16	2.2	-0.4
Heifer conception rate	-0.08	2.2	-0.2
Cow livability	-0.08	12	-1.0
Net merit \$	-25	1	-25

Example EFI adjustment for Acura

- Difference of EFI – daughter F = $8.7 - 0.0 = 8.7\%$
- Economic loss (future – past daughters) = $8.7 \times \$25/1\%F = \217
- Acura's initial NM\$ = **+\$1,282** before adjustment
- Acura's official NM\$ = **+\$1,065** after adjustment
- As the population becomes more related to an animal, its evaluations decrease
- Progeny, grandprogeny, etc., also adjusted because their EFIs tend to be higher than breed average

Opportunities and Conclusion

Conclusions

- **Male genetic diversity is very limited in the Holstein population**
- **It's important to conserve female genetic variation**
- **Inbreeding depression may be responsible for some of the decrease in fitness traits, such as fertility**
- **If stacking of pedigrees continues dairy breeding will come to resemble pig and chicken breeding – without the controlled environments**

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Questions?

