How Can We Design a Cow to Better Meet Human Needs?

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BLOG:https://biobeef.faculty.ucdavis.edu/

http://animalscience.ucdavis.edu/animalbiotech

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Breeders have selected for desired changes to our food and companion animal populations

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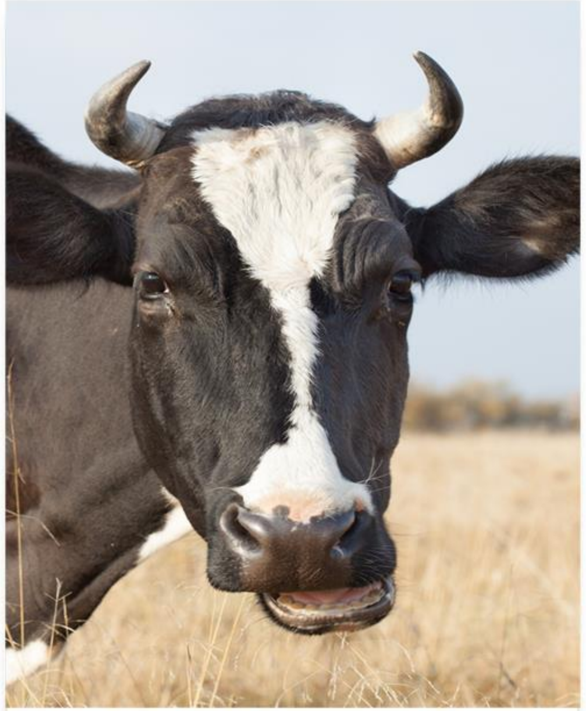
Animal breeders are glorified matchmakers

Back to Safari 15:15 41%

tinder



Jane

Loves grass, chewing, has nice big udders

ure https://www.stgen.com/sire-directory/dairy-bull-usa.aspx?code=029HO17553&language=english&title=uecker-supersire-josuper-et

Back | Catalog | Genomic | Proven | Red | Polled | CANADA | GERMAN | HISTORY

029HO17553 JOSUPER

Reg: HOUSA000070726929 RHA: 99% DOB: 01/26/2013 DMS: 345,234 aAa: 324 AE A1A2

Uecker Supersire Josuper-ET TC

Supersire x Beacon x Jango

04/2018	CDCB SUMMARY - MACE			NM$ +998
Milk	+3442	99%R	Fluid Merit $	+1010
Fat	+114	-0.05%	Cheese Merit $	+996
Protein	+98	-0.02%	Grazing Merit $	+880
SCS	2.83	98%R	F Effic. +260	Fert. Index -0.1
PL	+6.1	88%R	Livability +2.3	73% Rel
DPR	-0.7	94%R	EFI 8.1% gEFI 8.8%	
HCR	+0.5		31273m 0.4% 1276f 0.3% 1004p	
CCR	+1.6		3022 Dtrs 601 Herds 77% US	

04/2018 CALVING SUMMARY			SCE 7.3 %
Sire Calving Ease	7.3%	99%R	17389 Obs
Daughter Calving Ease	3.9%	98%R	1053 Obs
Sire Stillbirth	6.4%	99%R	15828 Obs
Daughter Stillbirth	3.9%	97%R	1029 Obs

04/2018 HA TYPE SUMMARY TPI +2806

PTAT +1.42 99%R UDC+0.94 FLC-0.19 BSC +1.00 769 D / 275 H

Stature	+1.16	Tall
Strength	+1.22	Strong
Body Depth	+0.61	Deep
Dairy Form	+0.74	Open Rib
Rump Angle	-0.19	High Pins
Thurl Width	+0.91	Wide
Rear Legs-Side View	+0.70	Sickle
Rear Legs-Rear View	-0.43	Hock In
Foot Angle	+0.27	Steep
Feet & Legs Score	+0.15	High
F. Udder Attachment	+0.68	Strong
Rear Udder Height	+2.33	High
Rear Udder Width	+2.14	Wide
Udder Cleft	+0.67	Strong
Udder Depth	-0.20	Deep
Front Teat Placement	-0.03	Wide
Rear Teat Placement	+0.11	Close
Teat Length	-0.04	Short

Sire: Seagull-Bay Supersire-ET TV TL TY TD
Dam: Uecker Beacon Joyfully-ET EX-90
04-04 2x 365d 36030m 3.7 1340f 3.2 1143p
MGS: End-Road Beacon-ET TV TL TY VG-85
MGD: Uecker Jango Joyful-ET EX-91
04-04 2x 365d 40340m 3.6 1454f 3.2 1281p
MGGS: Jango-ET TV TL
MGGD: Uecker Oman Jodee TV VG-86 GMD DOM
04-09 2x 365d 50750m 4.3 2171f 3.1 1572p

Dam: Uecker Beacon Joyfully-ET

match.com

IT ALL STARTS WITH A DATE

Similar ST Bulls

NAAB	NAME	PTAM	CFP	DPR	UDC	FLC	SCE
147HO02424	Sargeant	2454	110	-0.7	1.51	0.73	7.1
224HO02881	Supershot	2185	119	1.7	1.10	0.52	6.9
224HO02982	Superstyle	2085	119	0.0	0.81	0.76	7.0

Proof History | Naab History | Top 100

PROOF	S	TPI	PTAM	MDtr	PTAT	UDC	FLC	TDtr	SCE
201804	A	2806	3442	3022	1.42	0.94	-0.19	769	7.3
201712	A	2757	3209	1562	1.36	1.03	-0.36	374	7.3
201708	A	2728	3129	662	1.21	0.83	-0.02	156	7.4
201704	A	2623	2633	90	1.37	0.71	0.58	10	7.0
201612	G	2580	2412	0	1.30	0.76	0.46		7.1
201608	G	2584	2461	0	1.36	0.76	0.50		7.1
201604	G	2597	2471	0	1.36	0.79	0.47		7.1
201512	G	2628	2493	0	1.41	0.82	0.47		7.5
201508	G	2630	2496	0	1.44	0.77	0.64		6.7
201504	G	2585	2426	0	1.60	0.92	0.61		6.9

More History ...

Proof Sons

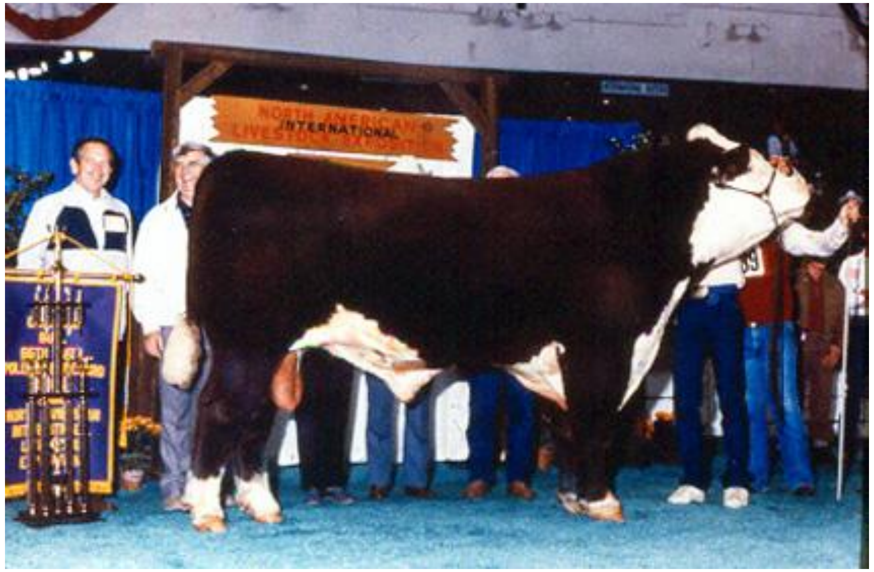
NAAB	TPI	NM	PTAM	PTAT	UDC	FLC	SCE
522HO03556	2795	877	2612	2.21	2.09	1.26	7.2
007HO12868	2780	930	1978	2.05	2.13	1.23	7.3

Beef Cattle Champions 1950s vs 1980s

1953. Grand Champion Angus Female

1950. Grand Champion Steer, weighing 1025 lbs

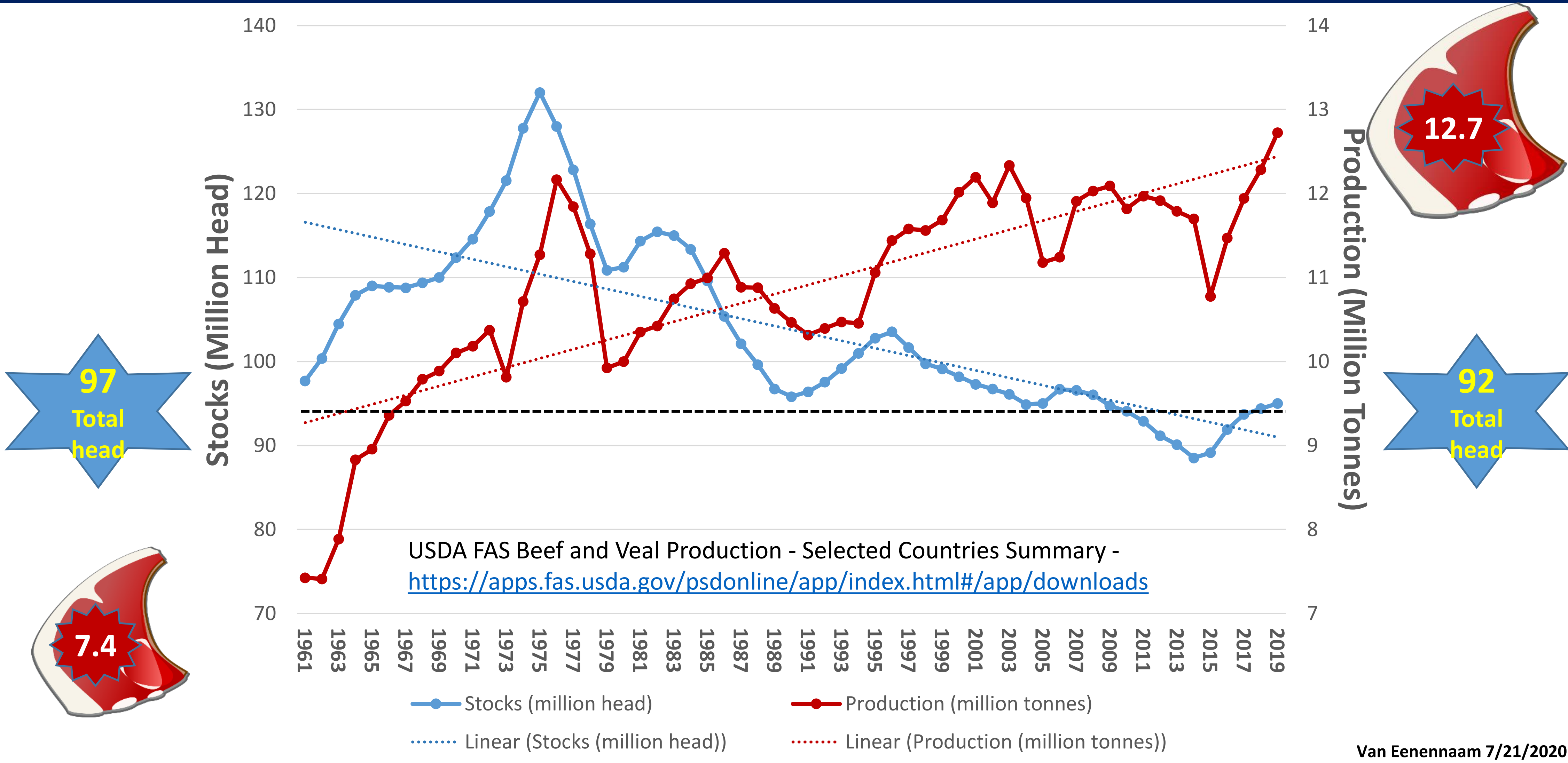
1986. Denver Champion weighing 2529 lbs



1988 Grand Champion Polled Hereford Show

US Cattle Inventory 1961 – 2019

Stocks Down (Million head; blue, left)
vs. Beef Production Up (Million Tonnes; red, right)



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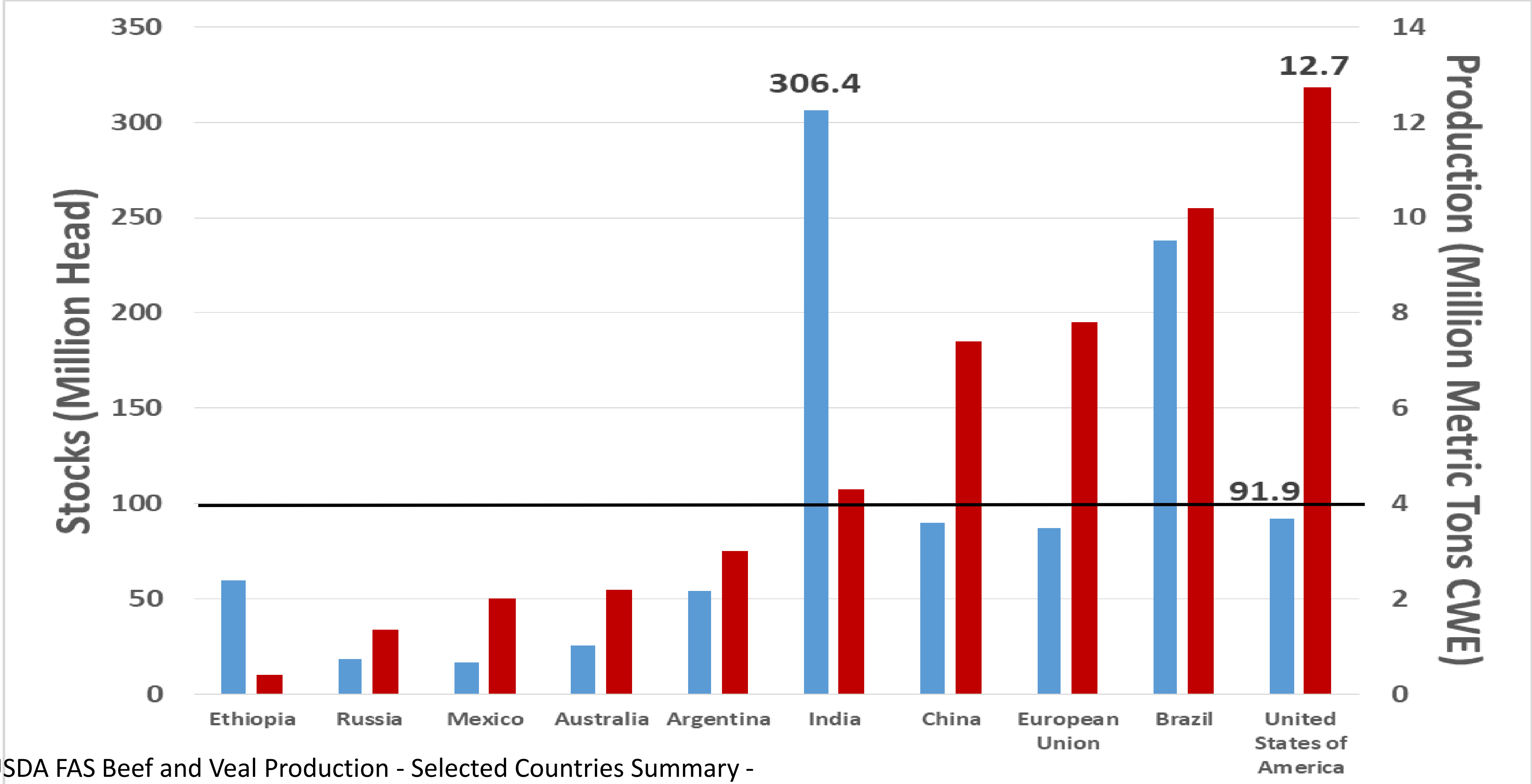
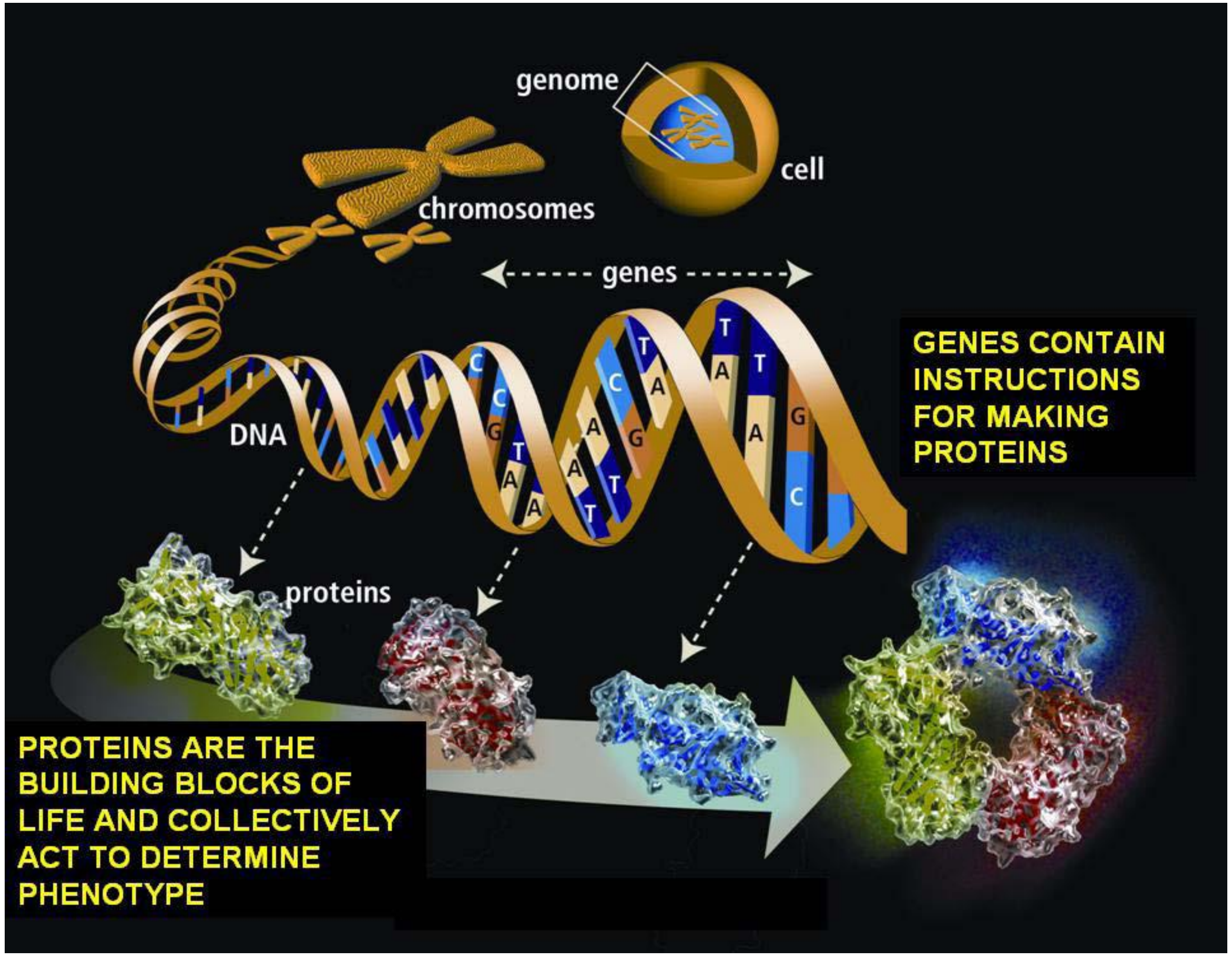
2019 Global Beef Production Numbers

Cattle numbers (Million Head; blue, left)
vs. Beef production (Million Tons; red, right)



USDA FAS Beef and Veal Production - Selected Countries Summary -
https://apps.fas.usda.gov/psdonline/app/index.html#/app/downloads

The bovine genome is similar in size to the genomes of humans, with an estimated size of 3 billion base pairs.



Human & cattle genomes are 83% identical

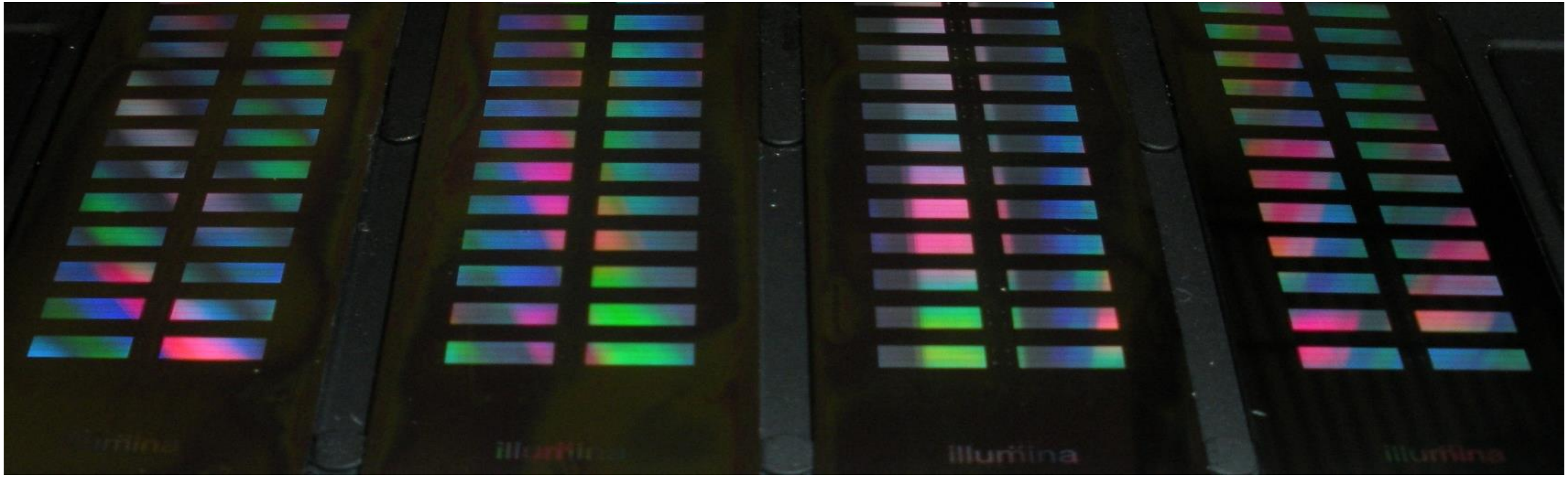
> 86.5 million genomic alterations (SNPs; Indels) between different breeds of cattle

1000 Bull Genomes Project: International consortium sequenced 2703 cattle to 11x fold coverage

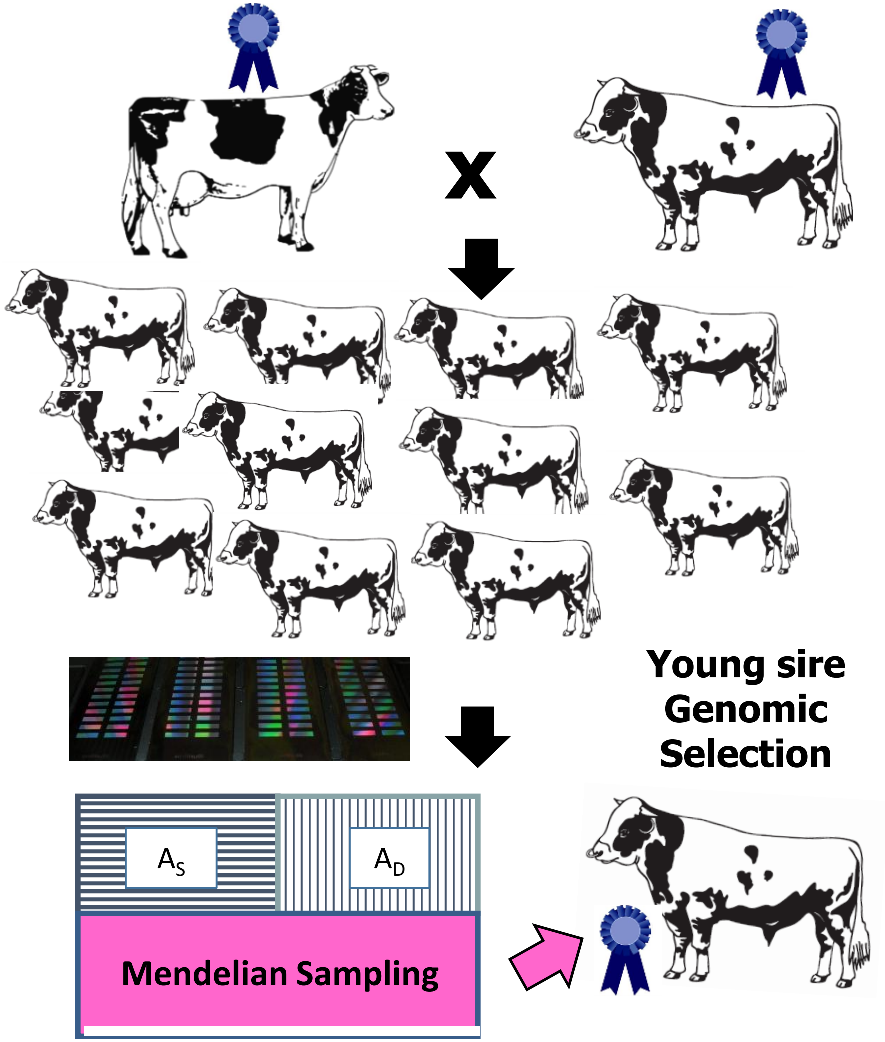
Hayes, B. J. & Daetwyler, H. D. 2018. 1000 Bull Genomes Project to Map Simple and Complex Genetic Traits in Cattle: Applications and Outcomes. Annual Review of Animal Biosciences 7:1.

High-throughput genotyping technology enabled the development of high density "SNP chips"

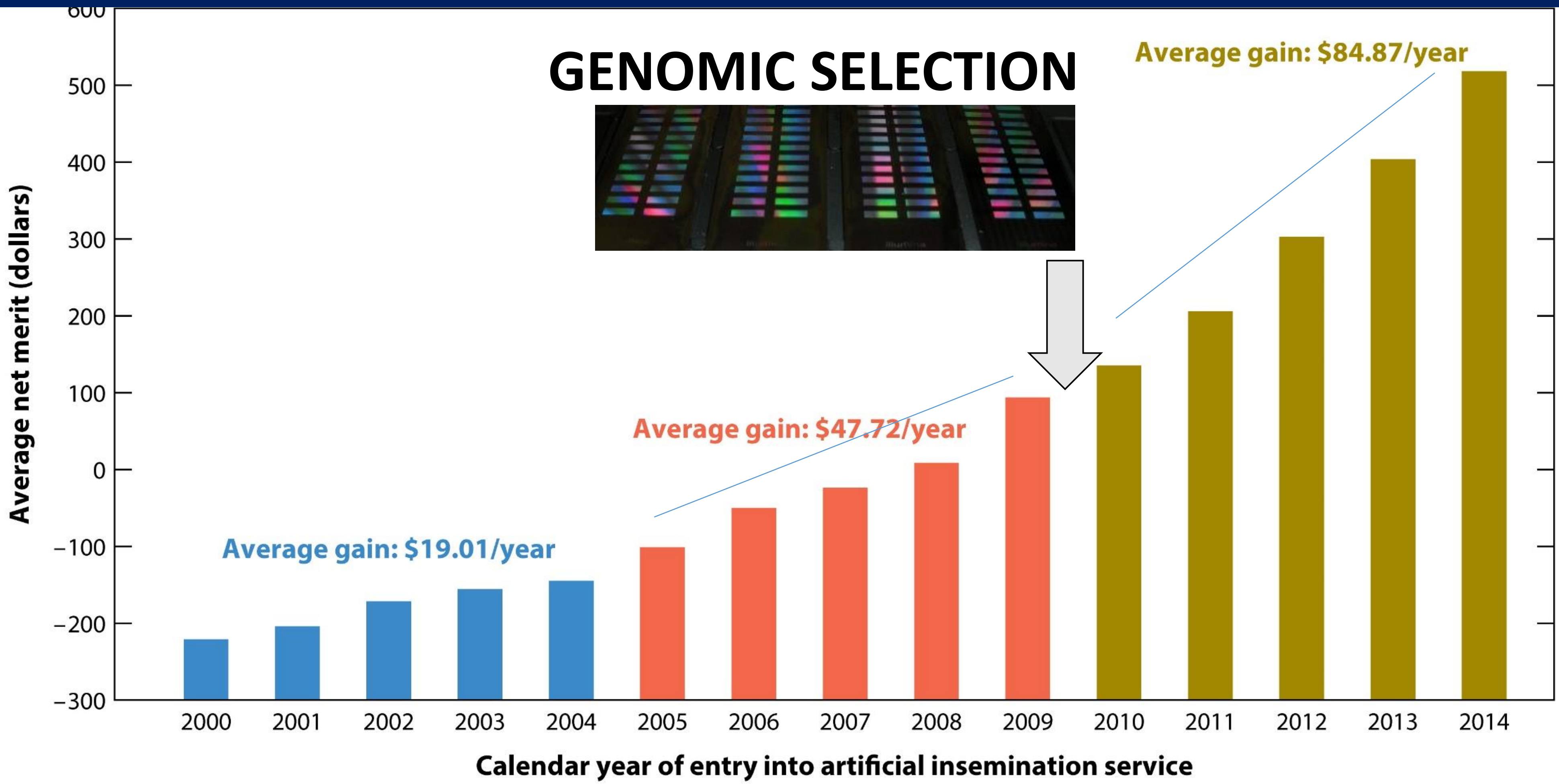
The 2009 sequencing of the bovine genome allowed for the development of a 50,000 SNP chip, also known as the "50K". Very rapidly adopted by the global cattle breeding community



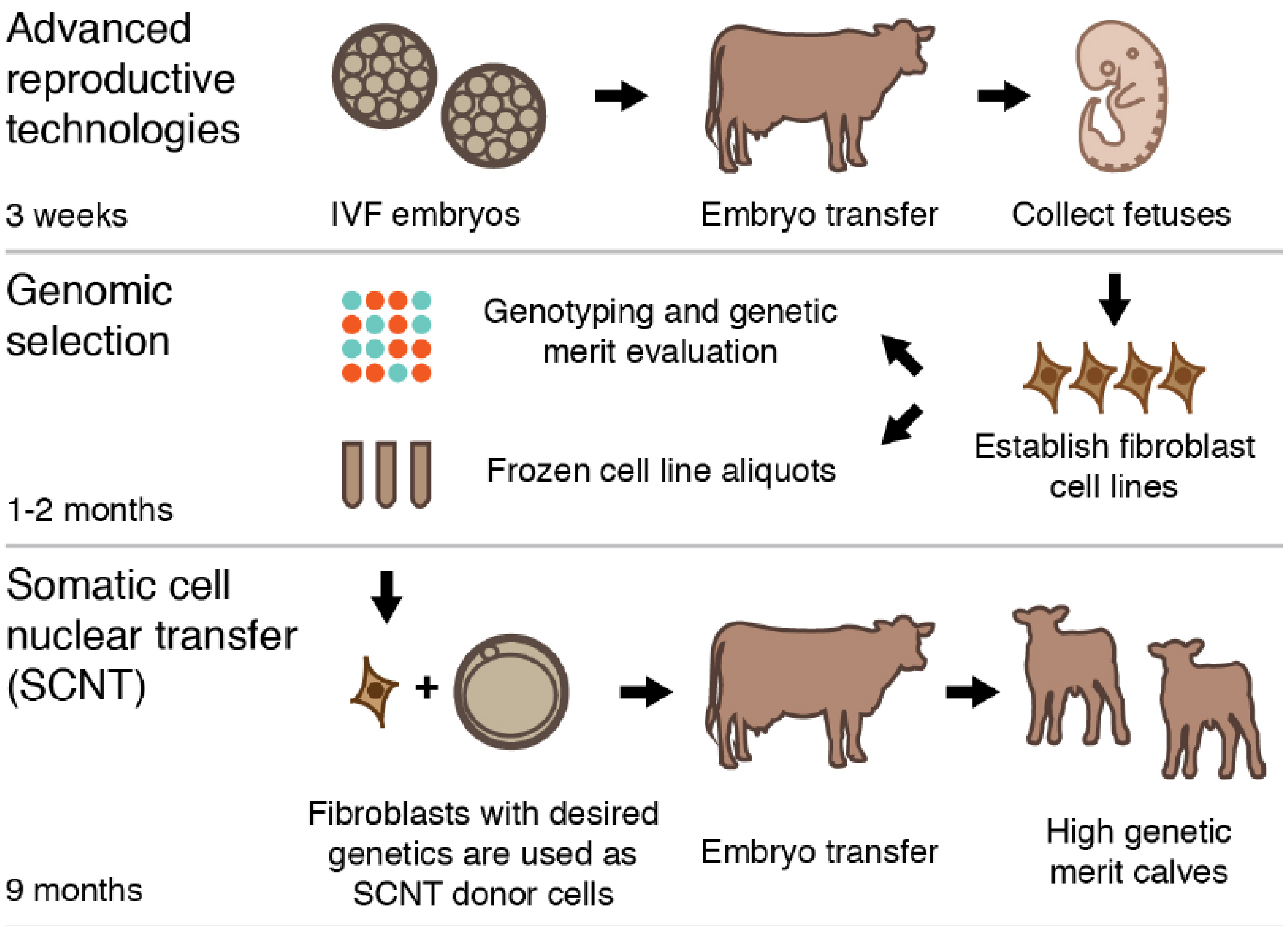
Genomic selection enables an early look at who got lucky in the roulette of Mendelian sampling



The rate of improvement in average net merit has nearly doubled for Holstein bulls since the implementation of genomic evaluation in 2010.



Wiggans, G. R., Cole, J. B., Hubbard, S. M., & Sonstegard, T. S. (2017). **Genomic selection in dairy cattle: the USDA experience.** *Annual review of animal biosciences*, *5*, 309-327.



Kasinathan, P. *et al.* 2015. Acceleration of genetic gain in cattle by reduction of generation interval. Sci. Rep. 5, 8674; DOI:10.1038/srep08674

The rate of genetic gain depends upon the four components of the breeders' equation

$$\textbf{Genetic change per year} = \frac{\textbf{(Accuracy x Intensity x Genetic Variation)}}{\textbf{Generation Interval}}$$

Accuracy = how certain we are about an animal's true genetic merit
Intensity of selection = fraction of animals selected as parents
Genetic variation = variation available in the population
Generation interval = time between generations

<u>Genetic engineering</u> (GE) the manipulation of an organism's genes by introducing, eliminating, or rearranging specific genes using the methods of modern molecular biology, particularly recombinant deoxyribonucleic acid (rDNA) techniques

Staph. aureus mastitis-resistant cows
(inflammation of mammary gland)

Nature Biotechnology 23:445-451. **2005**

nature biotechnology

ARTICLES

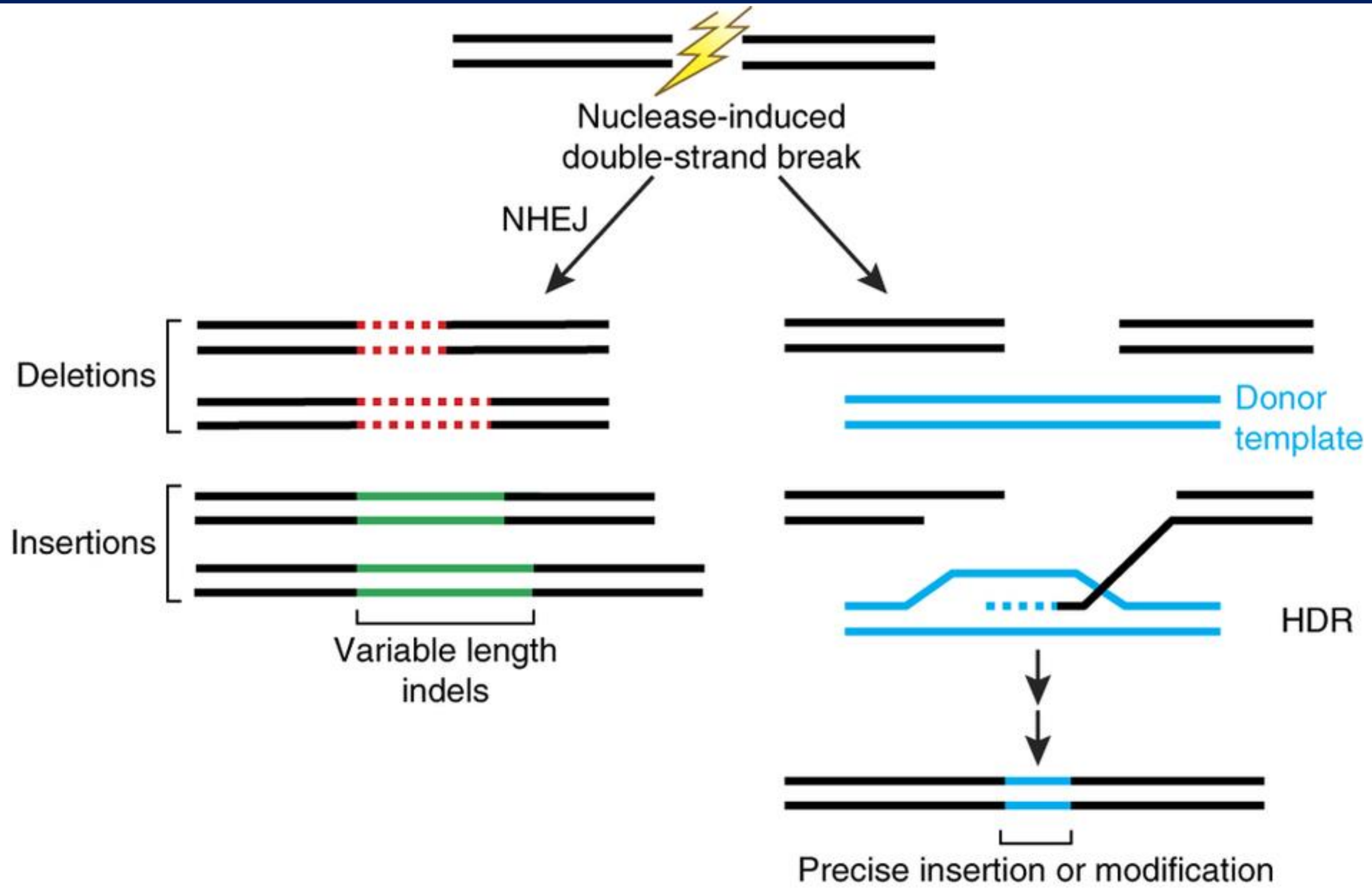
Genetically enhanced cows resist intramammary *Staphylococcus aureus* infection

Robert J Wall[1], Anne M Powell[1], Max J Paape[2], David E Kerr[3], Douglas D Bannerman[2], Vernon G Pursel[1], Kevin D Wells[4], Neil Talbot[1] & Harold W Hawk[1]

Mastitis, the most consequential disease in dairy cattle, costs the US dairy industry billions of dollars annually. To test the feasibility of protecting animals through genetic engineering, transgenic cows secreting lysostaphin at concentrations ranging from 0.9 to 14 mg/ml in their milk were produced. *In vitro* assays demonstrated the milk's ability to kill *Staphylococcus aureus*. Intramammary infusions of *S. aureus* were administered to three transgenic and ten nontransgenic cows. Increases in milk somatic cells, elevated body temperatures and induced acute phase proteins, each indicative of infection, were observed in all of the nontransgenic cows but in none of the transgenic animals. Protection against *S. aureus* mastitis appears to be achievable with as little as 3 mg/ml of lysostaphin in milk. Our results indicate that genetic engineering can provide a viable tool for enhancing resistance to disease and improve the well-being of livestock.

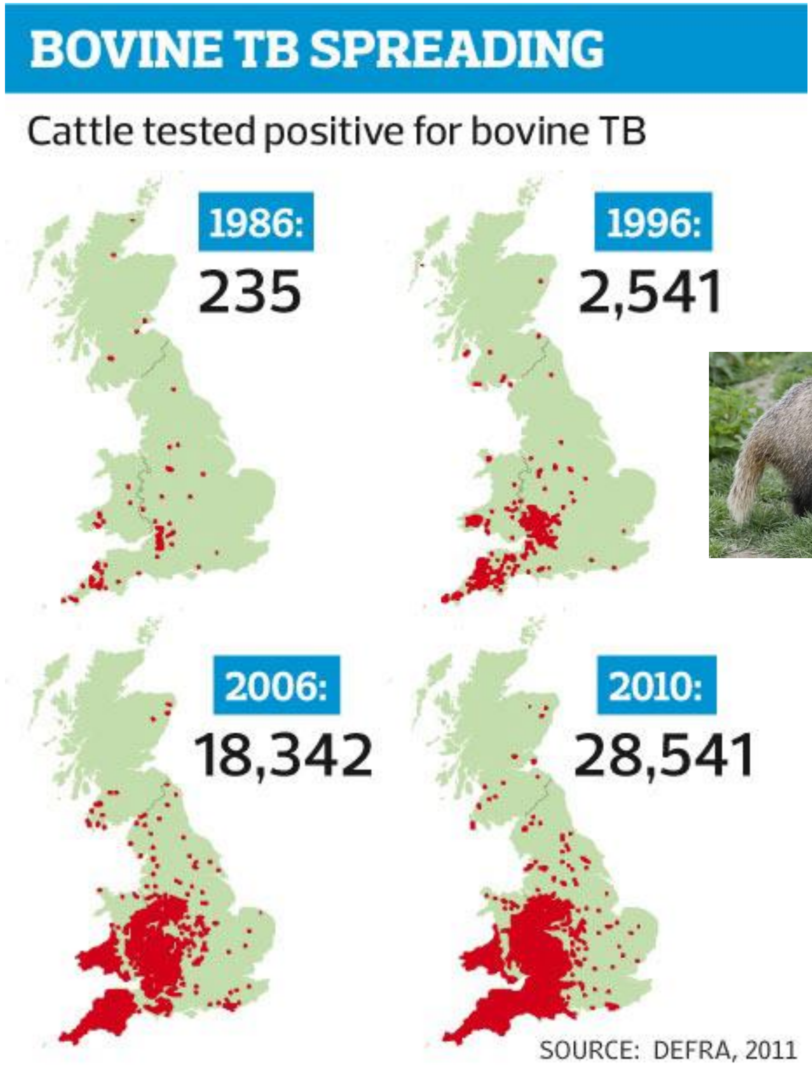
Lysostaphin from *Staphylococcus simulans*

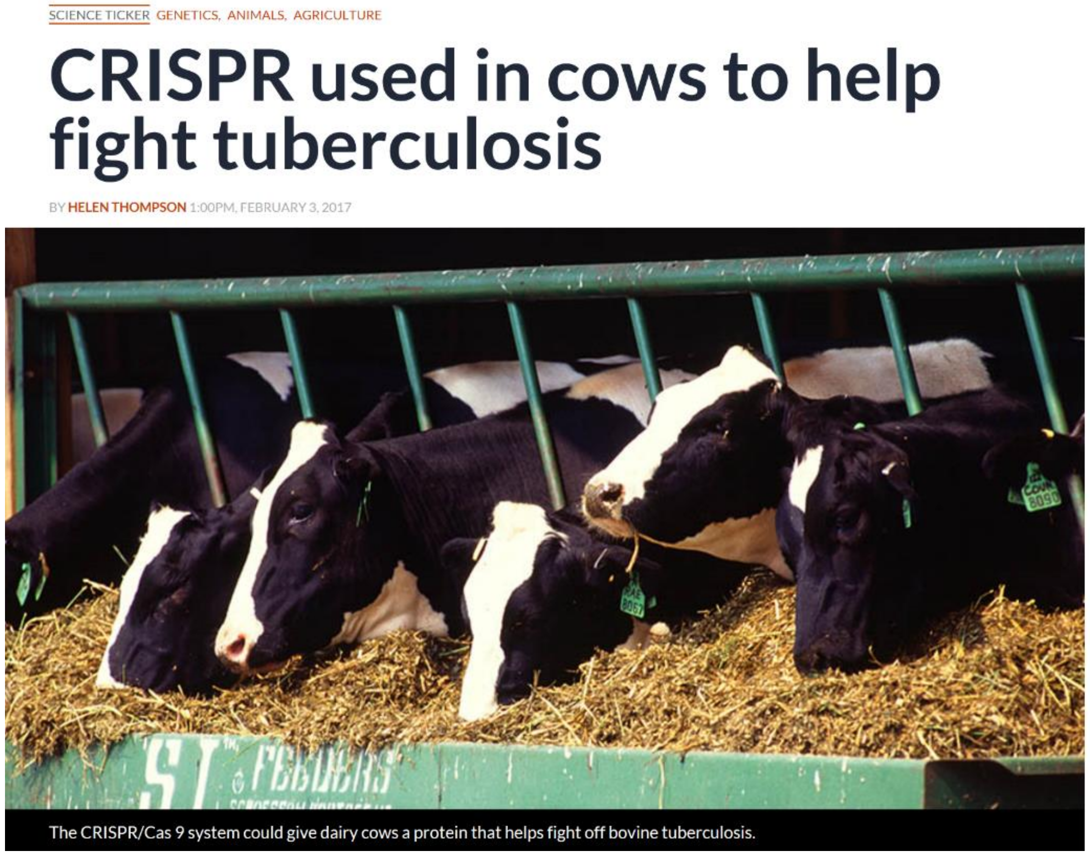
Gene editing involves introducing a double-strand break in the DNA at a targeted location in the genome



Sander JD, Joung JK. CRISPR-Cas systems for editing, regulating and targeting genomes. *Nat Biotech* 2014;32:347-355.

Gene editing to produce Tuberculosis resistant cattle





Gao et al. 2017. **Single Cas9 nickase induced generation of NRAMP1 knockin cattle with reduced off-target effects**. Genome Biol. Feb 1;18(1):13.
Northwest A&F University, Yangling, China

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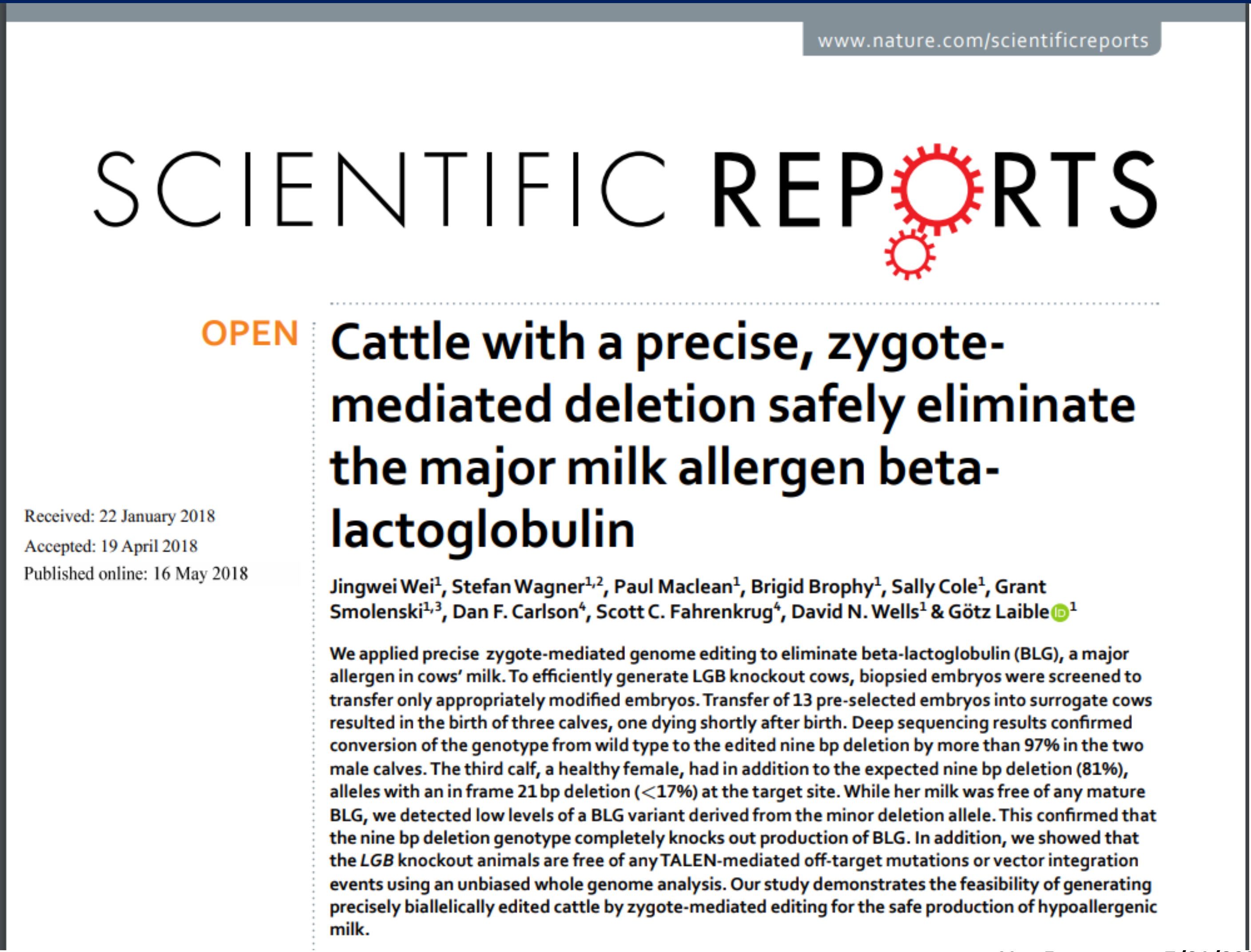
Genetic improvement (permanent, cumulative) as a solution to animal disease rather than antibiotics/chemicals

Gene editing to remove the major milk allergen: beta-lactoglobulin protein

Wei, J., Wagner, S., Maclean, P. *et al.* Cattle with a precise, zygote-mediated deletion safely eliminate the major milk allergen beta-lactoglobulin. *Sci Rep* **8,** 7661 (2018). https://doi.org/10.1038/s41598-018-25654-8



www.nature.com/scientificreports

SCIENTIFIC REPORTS

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Received: 22 January 2018
Accepted: 19 April 2018
Published online: 16 May 2018

Cattle with a precise, zygote-mediated deletion safely eliminate the major milk allergen beta-lactoglobulin

Jingwei Wei[1], Stefan Wagner[1,2], Paul Maclean[1], Brigid Brophy[1], Sally Cole[1], Grant Smolenski[1,3], Dan F. Carlson[4], Scott C. Fahrenkrug[4], David N. Wells[1] & Götz Laible[1]

We applied precise zygote-mediated genome editing to eliminate beta-lactoglobulin (BLG), a major allergen in cows' milk. To efficiently generate LGB knockout cows, biopsied embryos were screened to transfer only appropriately modified embryos. Transfer of 13 pre-selected embryos into surrogate cows resulted in the birth of three calves, one dying shortly after birth. Deep sequencing results confirmed conversion of the genotype from wild type to the edited nine bp deletion by more than 97% in the two male calves. The third calf, a healthy female, had in addition to the expected nine bp deletion (81%), alleles with an in frame 21 bp deletion (<17%) at the target site. While her milk was free of any mature BLG, we detected low levels of a BLG variant derived from the minor deletion allele. This confirmed that the nine bp deletion genotype completely knocks out production of BLG. In addition, we showed that the *LGB* knockout animals are free of any TALEN-mediated off-target mutations or vector integration events using an unbiased whole genome analysis. Our study demonstrates the feasibility of generating precisely biallelically edited cattle by zygote-mediated editing for the safe production of hypoallergenic milk.

How might gene editing be used in cattle breeding programs?

Target	Targeted Trait/Goal	Reference
Intraspecies *POLLED* allele substitution	No horns/welfare trait	Carlson et al., 2016
Intraspecies *SLICK* allele substitution	Heat tolerance	Sonstegard et al., 2017
Myostatin (MSTN) gene knockout	Increased lean muscle yield	Proudfoot et al., 2014
Beta-lactoglobulin gene knockout	Elimination of milk allergen	Yu et al., 2011
Prion protein (PRNP) knockout	Elimination of prion protein	Bevacqua et al., 2016
Intraspecies *CALPAIN* & *CAPASTATIN* allele substitution	Improved meat tenderness	Casas et al., 2006 (not reduced to practice)
Insertion of lysostaphin/lysozyme transgene	Resistance to mastitis	Liu et al., 2013 &2014
CD18 gene edit	Resistance to bovine respiratory disease	Shanthalingam et al., 2016
Insertion of SP110, NRAMP1	Resistance to tuberculosis	Wu et al., 2015; Gao et al., 2017
Intraspecies SRY translocation onto X chromosome	All male offspring	Owen et al., 2018
NANOS gene knockout	Infertile males (for gonial cell transfer)	Ideta et al., 2016

Updated and modified from Van Eenennaam, A. L. 2017. Current Opinion in Biotechnology. 44:27-34.

Gene editing of myostatin to obtain double muscle cattle versus conventional breeding

Naturally-occurring mutation in Belgian Blue

Is one way of obtaining the same mutation better than the other?

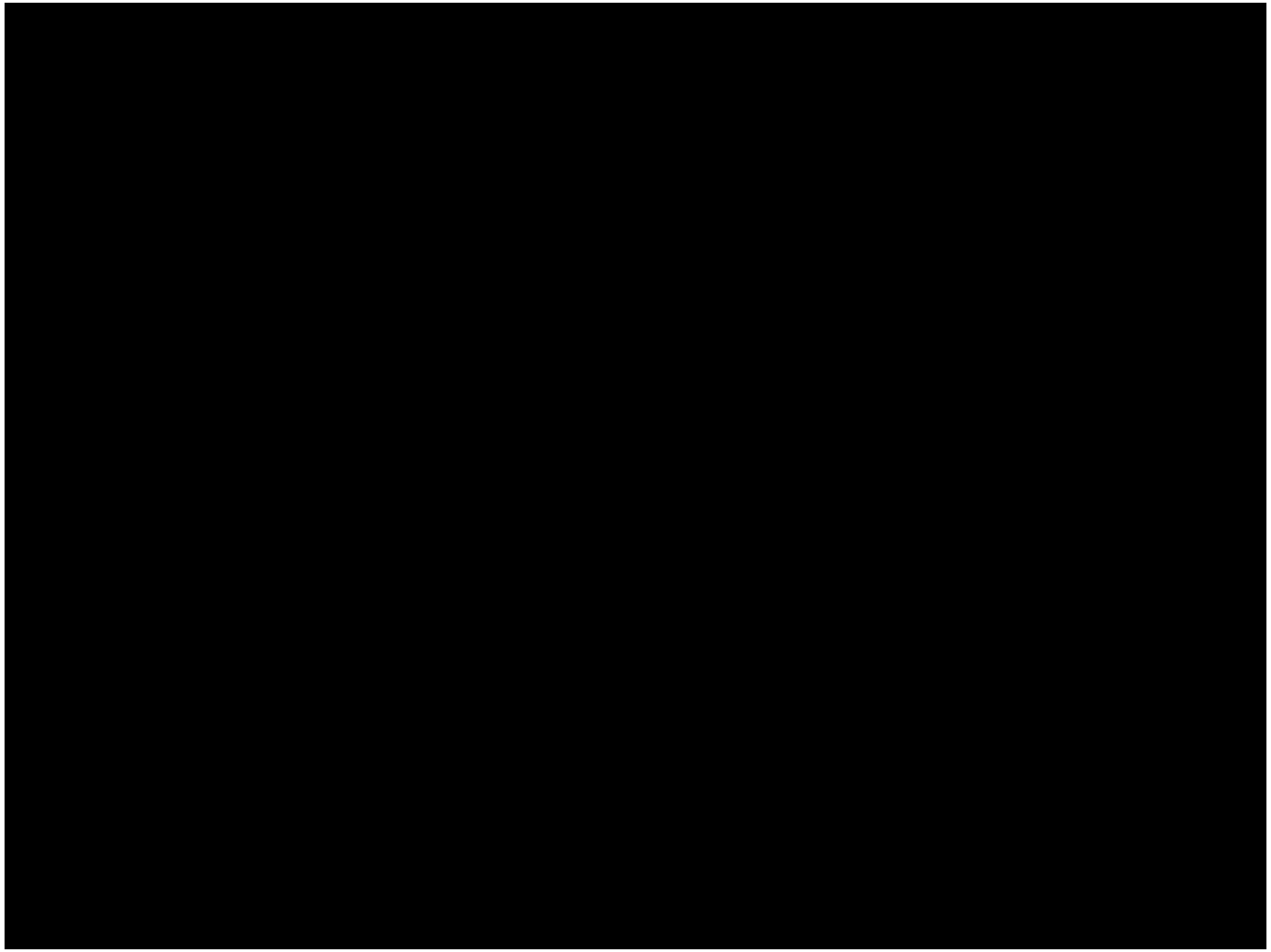
Proudfoot C, et al. 2015. Genome edited sheep and cattle. Transgenic Res. 2015 Feb;24(1):147-53.

Gene Edited Polled Calves

Naturally-occurring bovine allele at polled locus

Carlson DF, Lancto CA, Zang B, Kim E-S, Walton M, et al. 2016.
Production of hornless dairy cattle from genome-edited cell lines.
Nat Biotech 34: 479-81

Precision breeding offers a new alternative to dehorning
YouTube: https://youtu.be/-Qks_LMmodw



Gene Edited Polled Calves

Naturally-occurring bovine allele at polled gene

10 base pairs (p)

212 base pairs (P)

POLLED GENE

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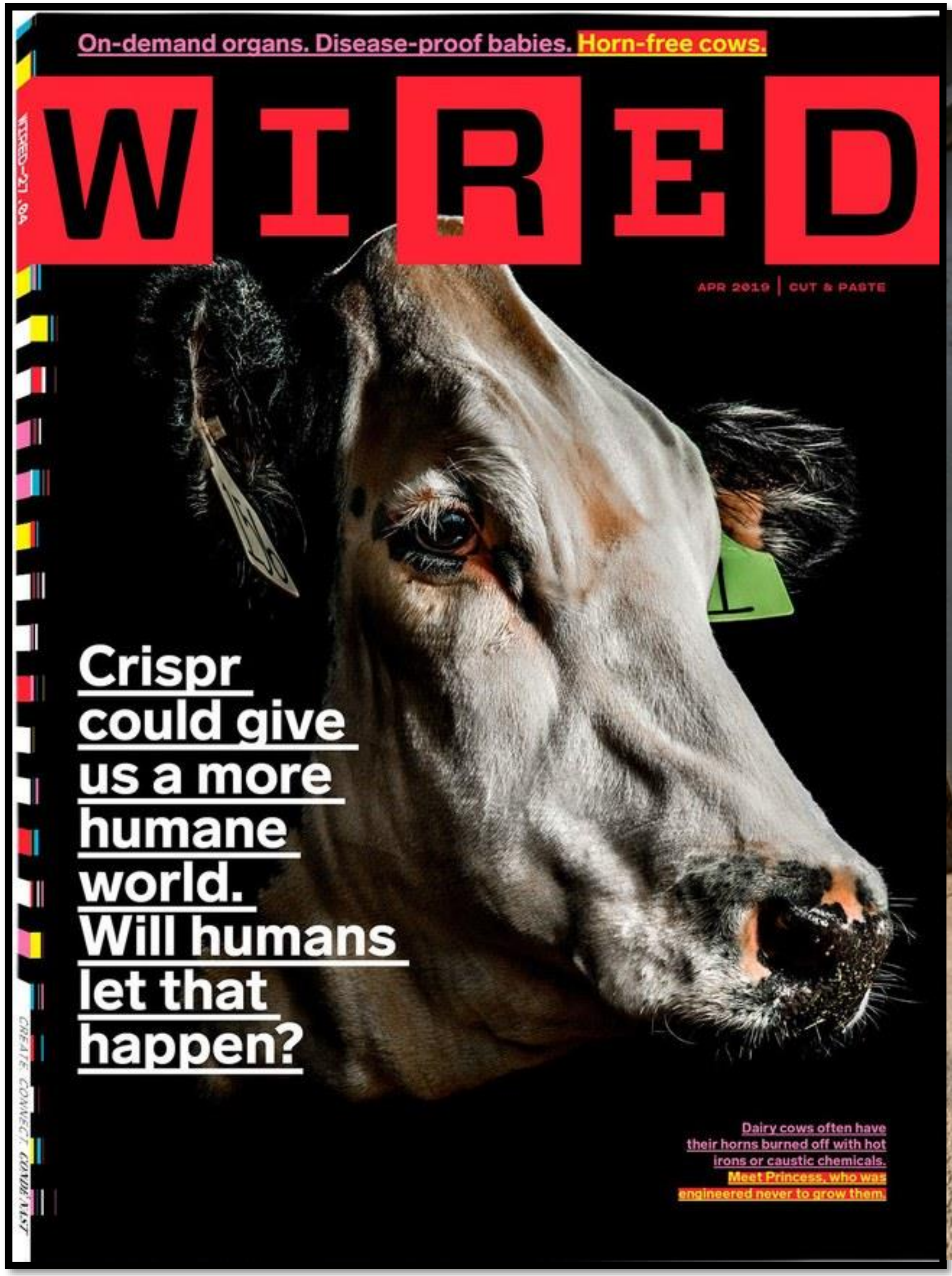
Even a female cow has to get "made up" for a glamor shot!

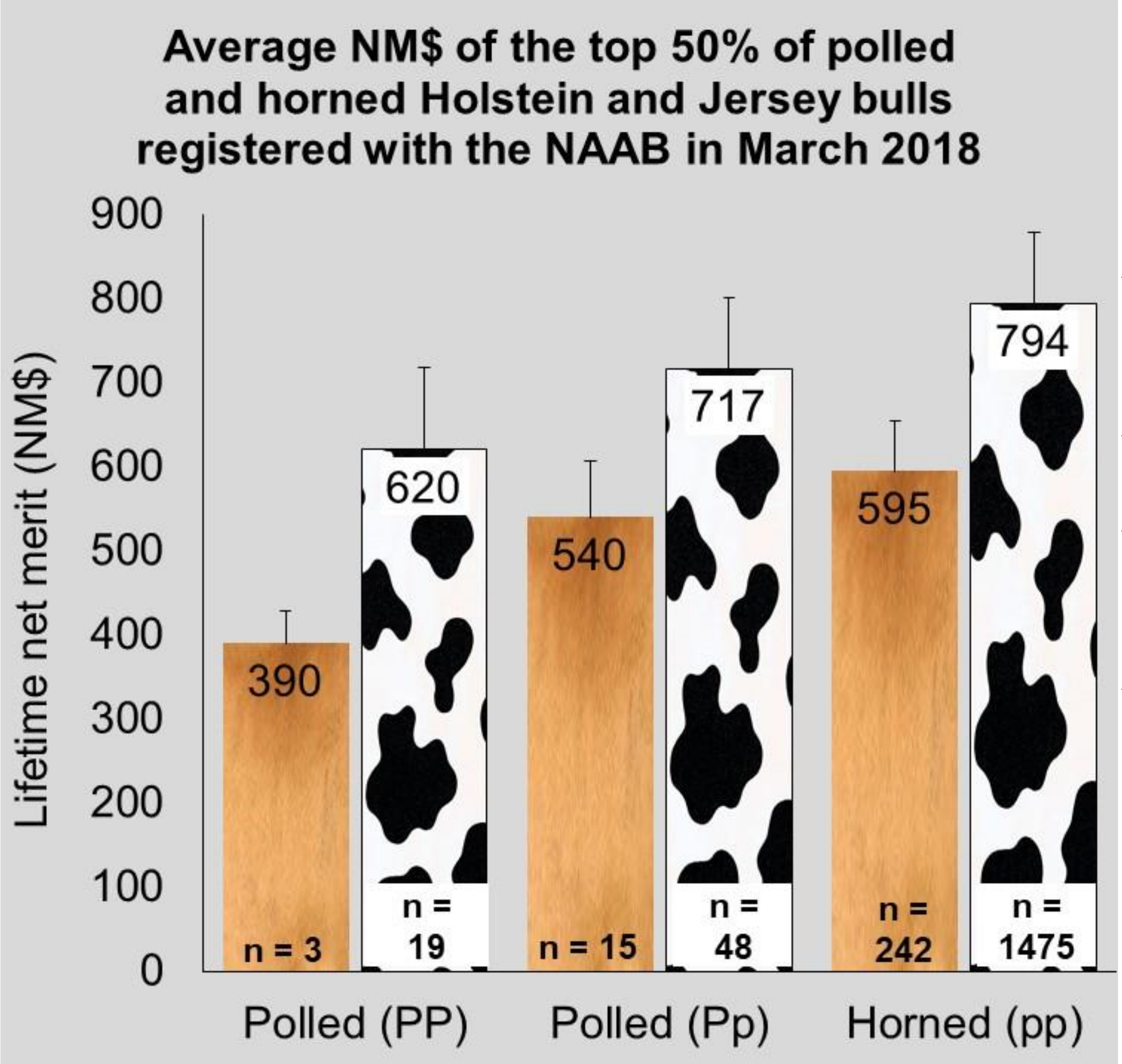
Princess gets her 15 minutes of fame



https://www.wired.com/story/crispr-gene-editing-humane-livestock 3/19/2019

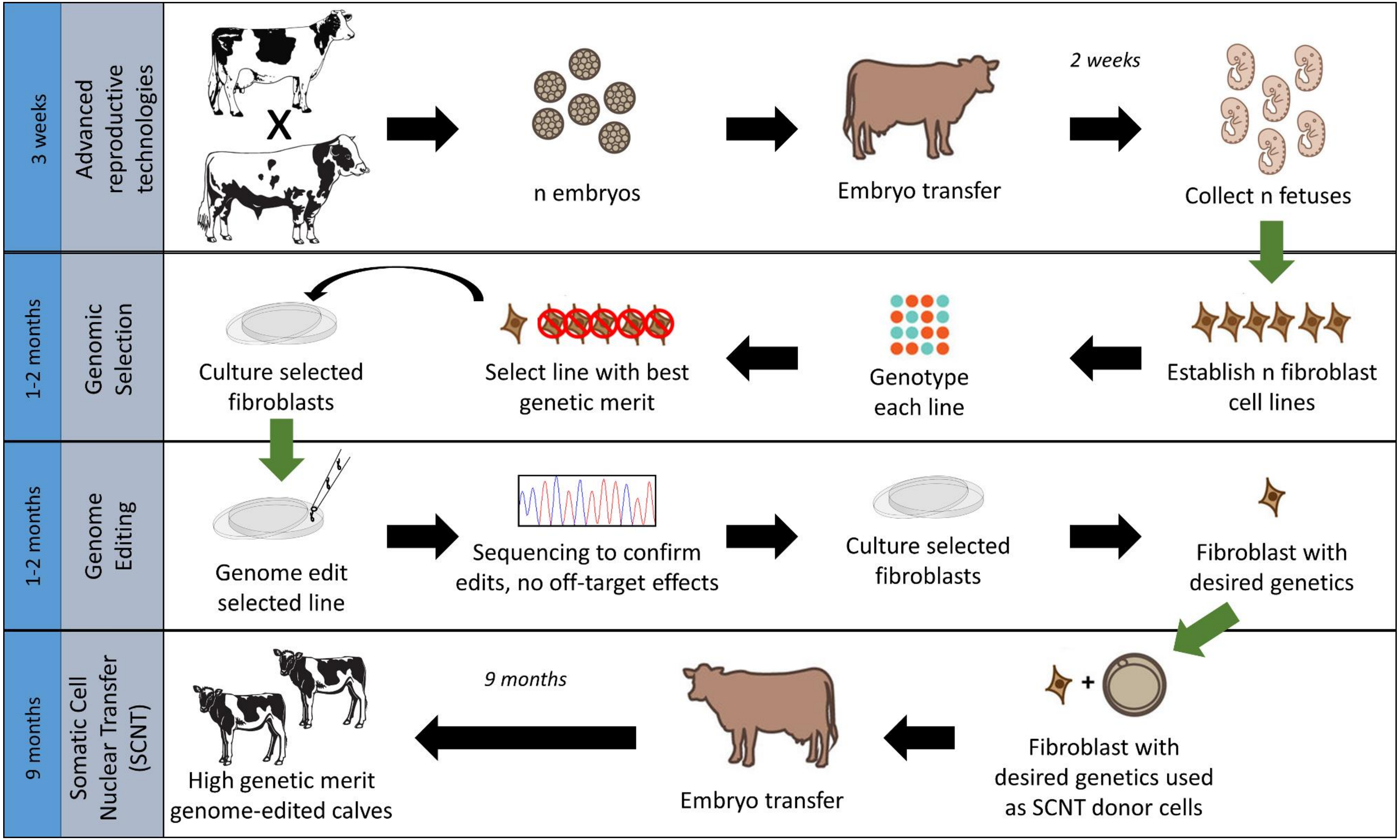
Winter is coming

Current polled dairy sires have inferior genetic merit



- ❖Daughters of polled Holstein sires will earn less over their lifetimes
- ❖**Polled allele frequency is 0.0071**
- ❖Adding polled to selection indices is not effective
- ❖If used exclusively polled sires would increase inbreeding & decrease genetic gain

Mueller, Maci et al. 2018. **Simulation of introgression of the POLLED allele into the Holstein breed via conventional breeding versus gene editing**. Proc. 11th World Congr. Genet. Appl. Livest. Prod., Auckland, New Zealand 11:755



Van Eenennaam, A. L. 2017. Genetic Modification of Food Animals. Current Opinion in Biotechnology. 44:27-34.

Editing as a Cherry on Top of the Breeding Sundae

It will be able to introduce useful alleles without linkage drag, and potentially bring in useful novel genetic variation from other species

Genome Editing

Somatic cell nuclear transfer cloning

Genomic Selection

Embryo Transfer

Artificial insemination

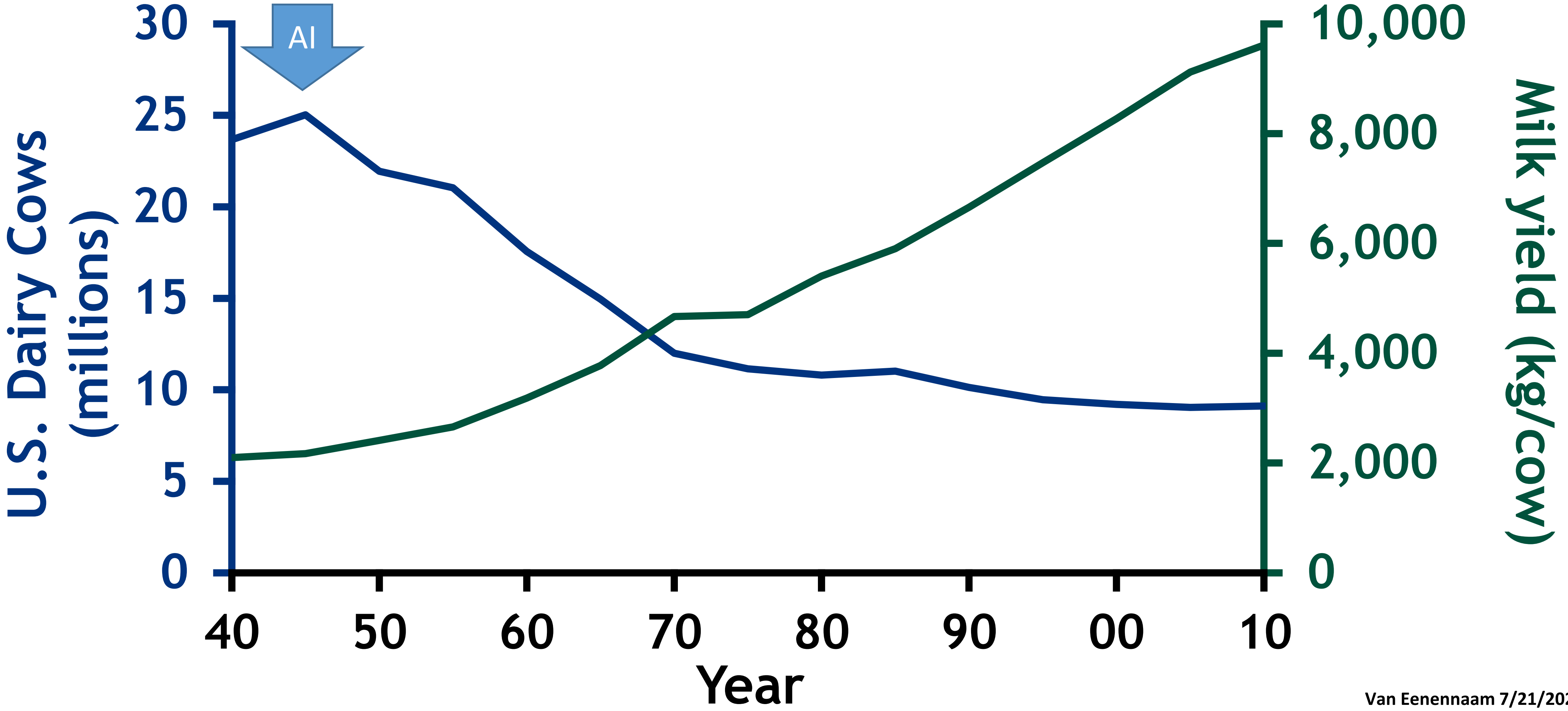
Progeny testing

Performance recording

Development of breeding goals

Association of like minded breeders

Be very aware of the trade offs associated with saying no to animal breeding innovations



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Can’t Stop the Feeding

YouTube: https://youtu.be/C0MBl0BANHg

Questions?

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My laboratory receives public funding support from the National Institute of Food and Agriculture and the Biotechnology Risk Assessment Grant (BRAG) program, U.S. Department of Agriculture, under award numbers 2017-33522-27097, 2018-67030-28360, and 2020-67015-31536.

USDA
United States Department of Agriculture
National Institute of Food and Agriculture