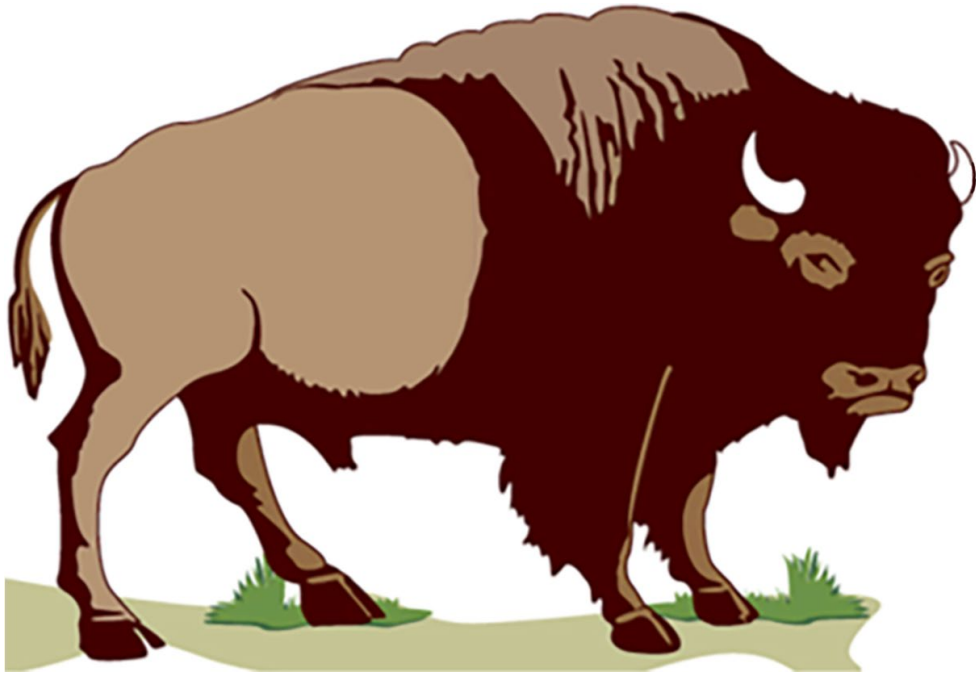


Progress report on Bison x Simmental F1 cross genome assembly

Mike Heaton, Ph.D.



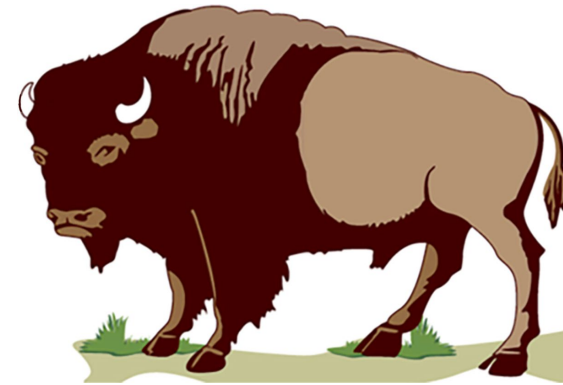
ASA Fall Focus Meeting
Sunday, 8:30, August 25, 2019
Manhattan, Kansas

Topics

- The problem of assembling a bovine genome



- Interspecies crosses for breed-specific genome assemblies

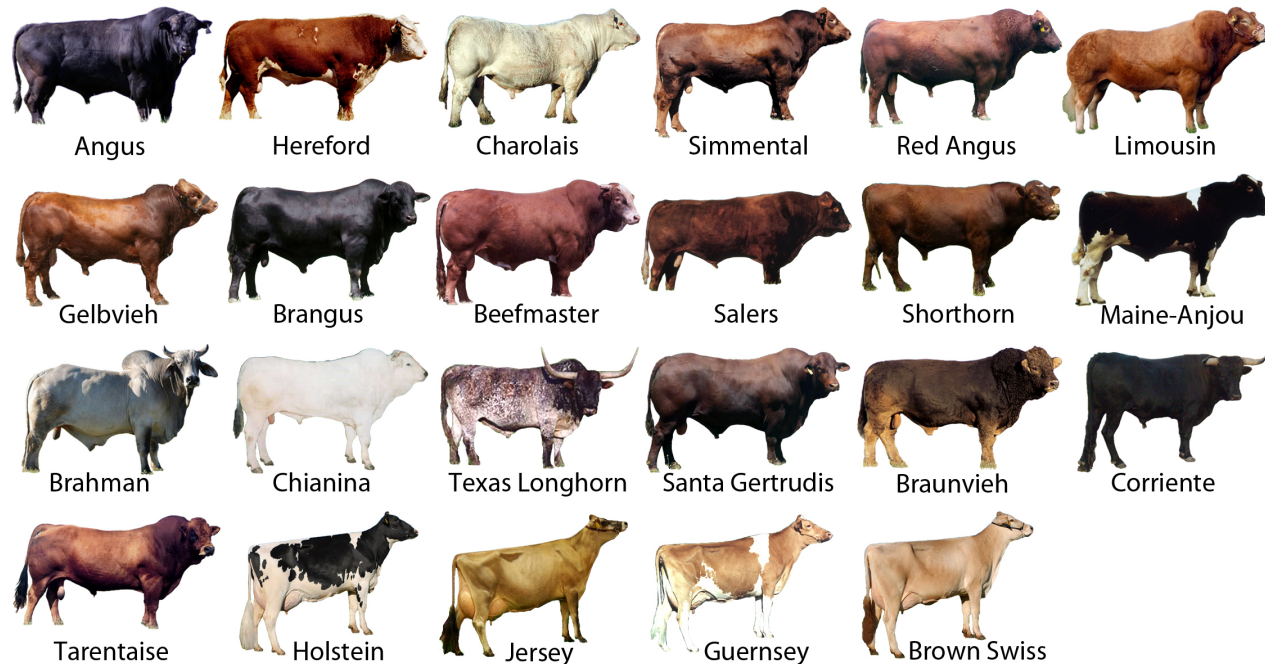


- Current status of the Simmental genome assembly



Why are breed-specific genome assemblies important?

- Required for understanding the functional genetic difference between breeds

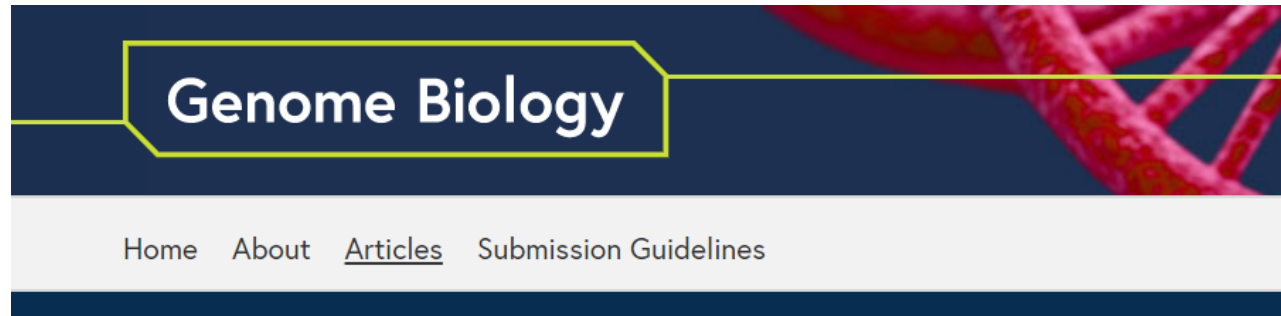


Hereford Line 1 Dominette 01449



- We cannot identify all that is unique about a breed by aligning it to a Hereford genome

In human genome research, efforts are underway to sequence ethnic groups



Research Highlight | [Open Access](#) | [Published: 24 May 2019](#)

One reference genome is not enough

[Xiaofei Yang](#), [Wan-Ping Lee](#), [Kai Ye](#) & [Charles Lee](#) 

Utah/Mormon

Chinese

Korean

African

Puerto Rican

Reference-quality cattle genomes are available today

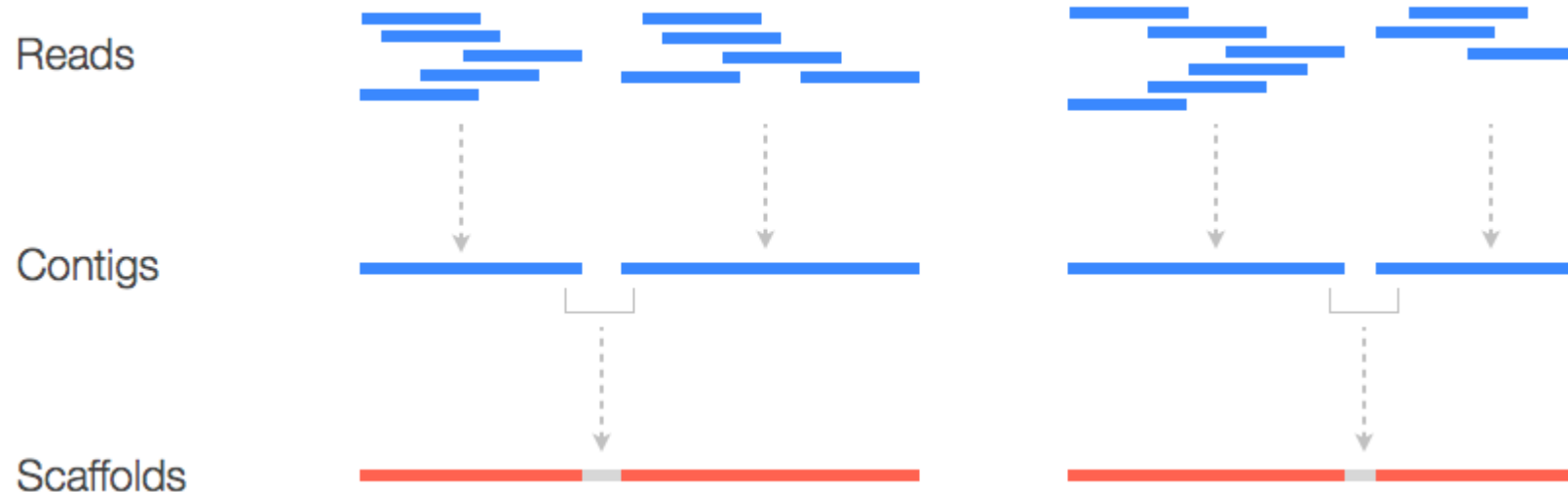
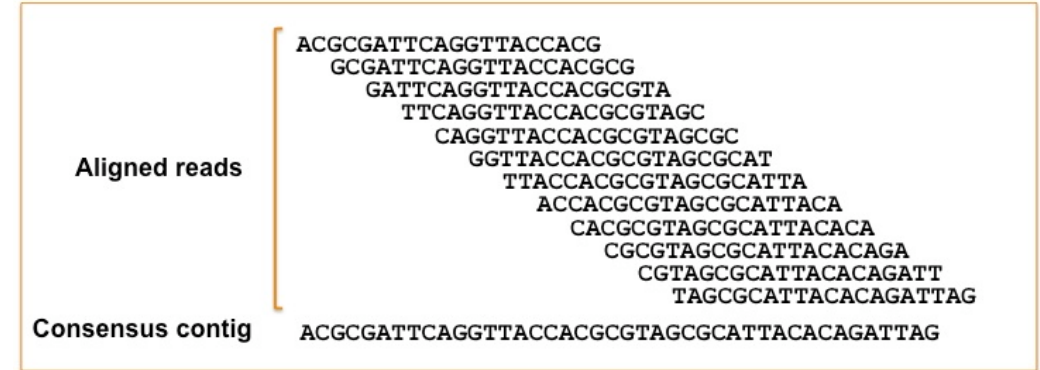
Hereford
Jersey
Holstein
Nelore
Angus
Brahman



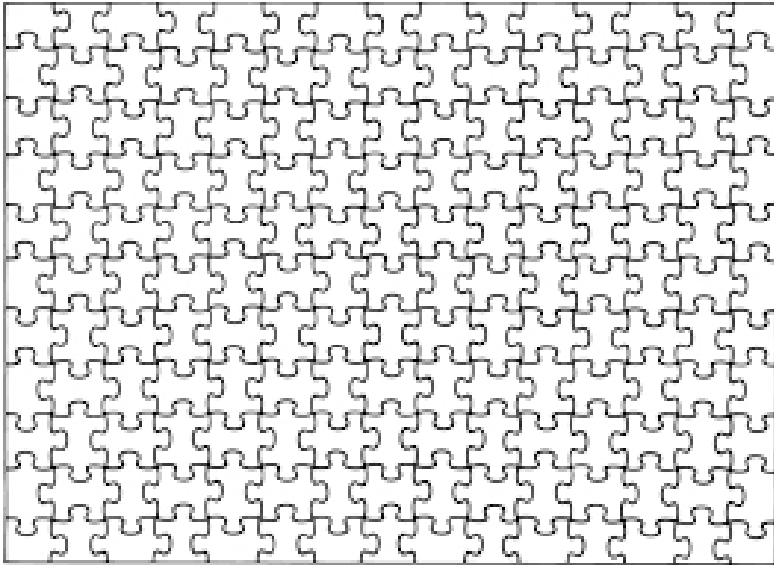
However, not all reference genomes are created equally

How to assemble a mammalian genome in two steps

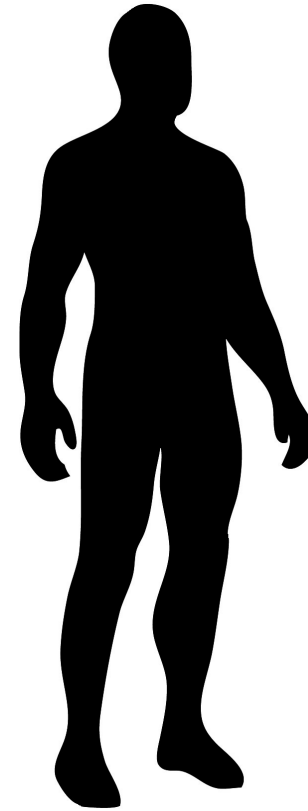
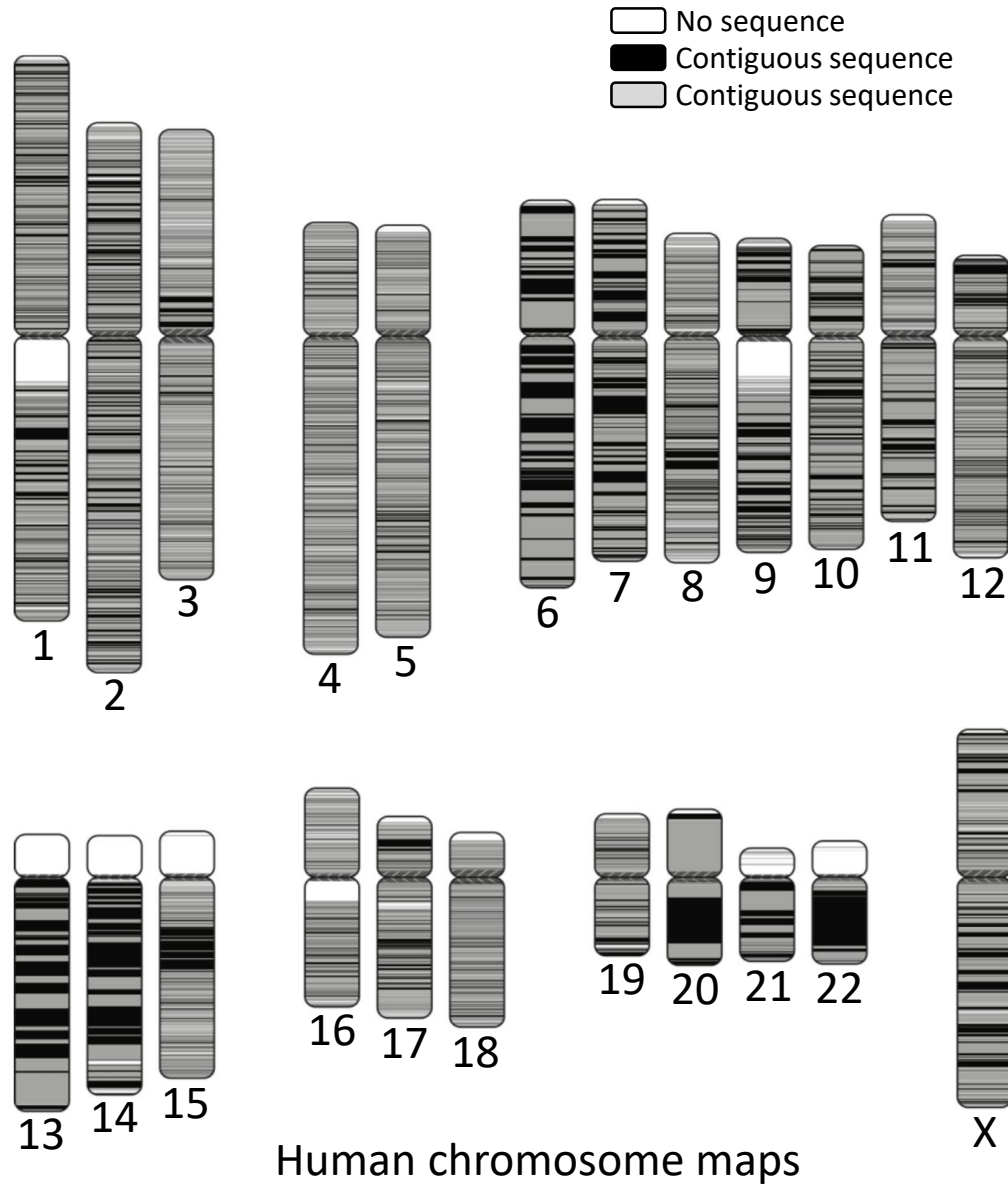
- Step 1: chop into short bits
- Step 2: align bits



The key to success: use long reads!



The issue of quality



- Human genome, 2001
- \$3 billion, 10 years
- “Short read” draft (90% complete)

International Human Genome Sequencing Consortium, Nature, 409:860–921 (2001)

Hereford reference assembly



- Bovine genome, 2009
- \$54 million, 7 years
- “Short read” draft (UMD3.1)
- 75,617 contigs

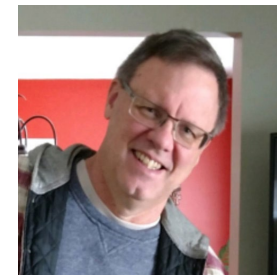
The Bovine Genome Sequencing and Analysis Consortium,
Science 2009 324:522-528

L1 Dominette 01449



- Bovine genome, 2018
- \$200,000, 3 years
- “Long read” (ARS-UCD1.2)
- 2,597 contigs

Rosen BD, et al. 2019, Submitted for review



Dr. Tim Smith

USDA Agricultural Research Service
U.S. DEPARTMENT OF AGRICULTURE

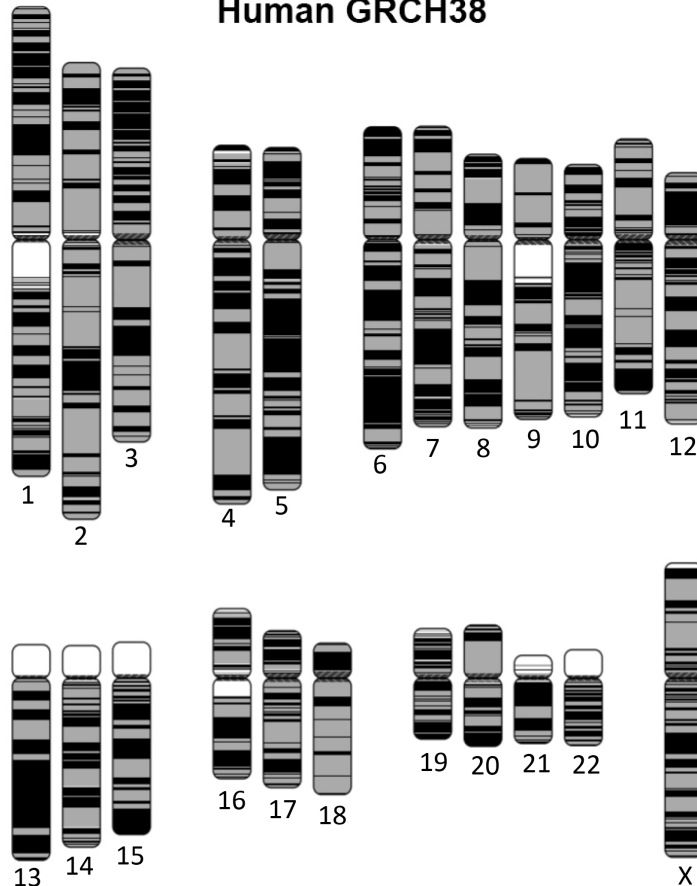
USMARC

Dr. Ben Rosen, ARS, Beltsville
Dr. Derek Bickhart, ARS, Madison
Dr. Bob Schnabel, U. Missouri
Dr. Sergey Koren, NHGRI
Dr. Juan Medrano, U.C. Davis

The most recent Hereford genome is better than that from humans



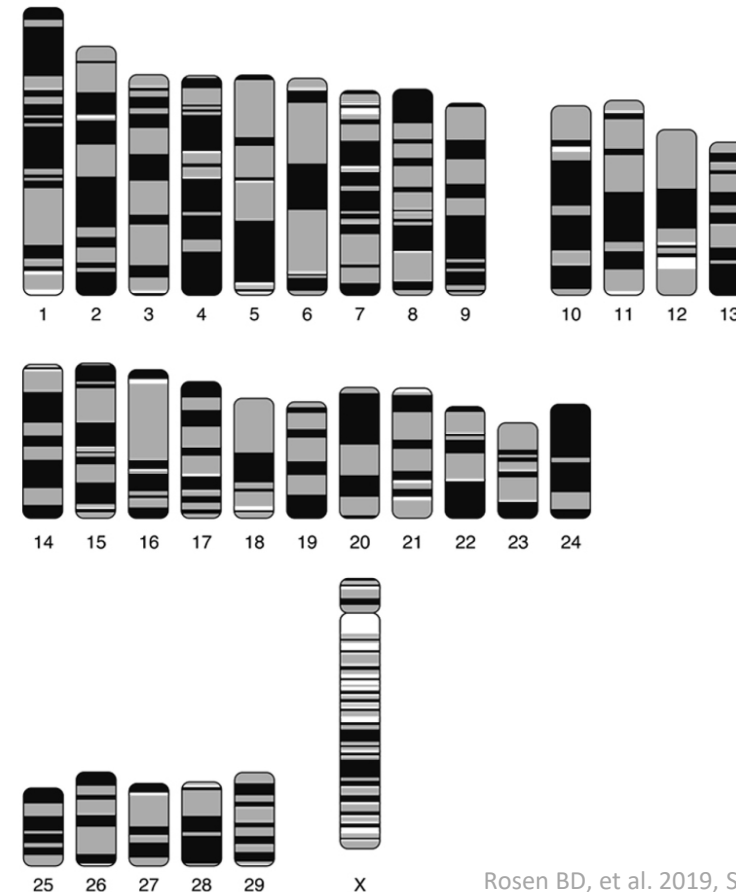
Human GRCH38



Ghurye J et al. 2019, PLoS Comput Biol 15(8): e1007273



Bovine Hereford ARS-UCDv1.2



Rosen BD, et al. 2019, Submitted for review

Most reference-quality genomes today are from line-bred animals

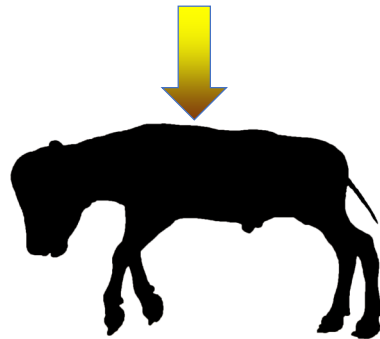
Dr. Tim Smith asked: “Why not use highly outbred animals?”

The trio-based method step 1 : create F_1

Koren S, et al. Nat Biotechnol. 2018 Oct 22. 10.1038/nbt.4277

Low et al., 2019, submitted for review.

Angus **X** Brahma
n



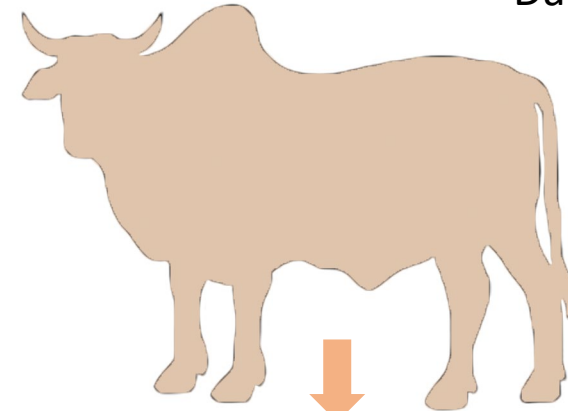
F_1 Angus x Brahman fetus (153 days)

Trio-binning

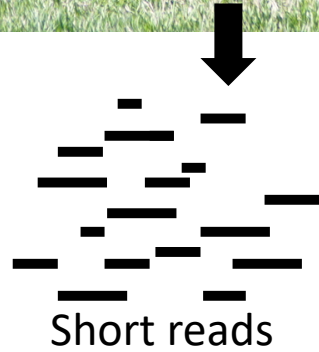
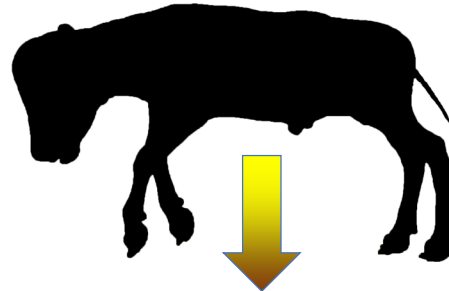
Sire



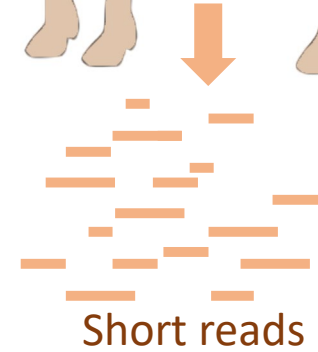
Dam



X



Short reads



Short reads



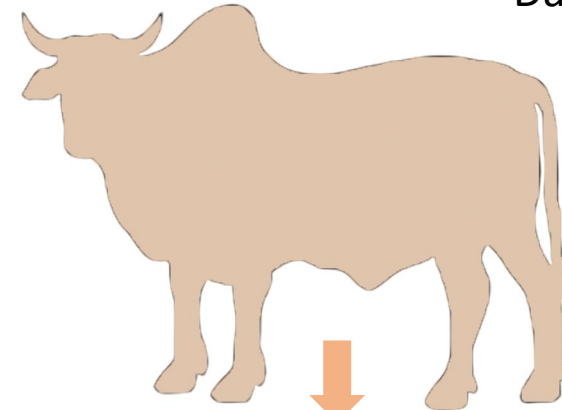
Long reads

Trio-binning

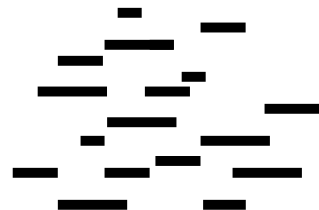
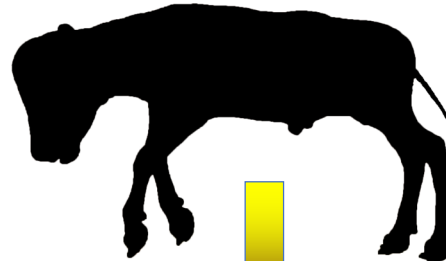
Sire



Dam



X



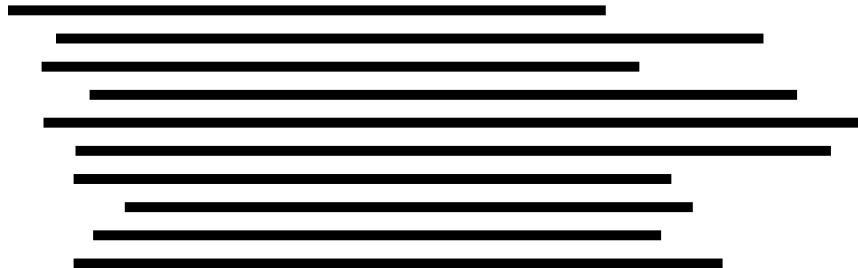
Short reads



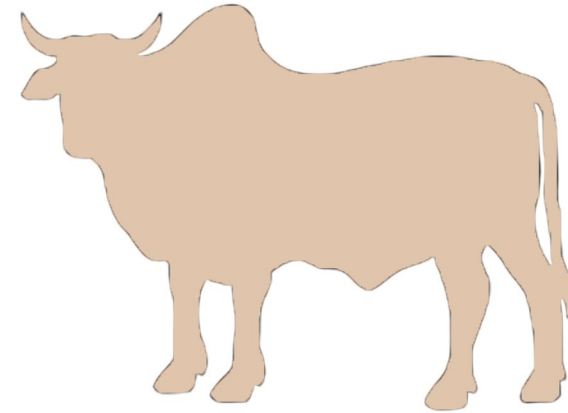
Short reads



Sort

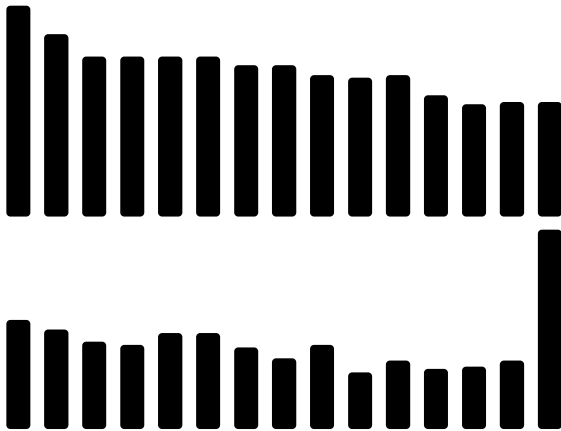


Trio-binning

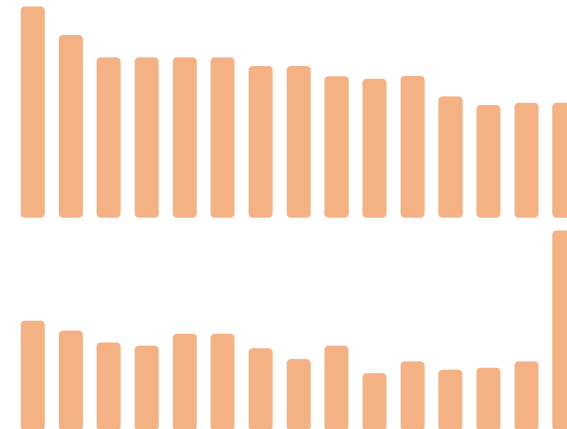


Assemble
separately

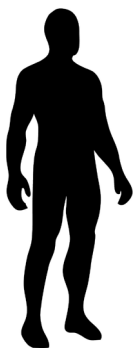
Angus assembly



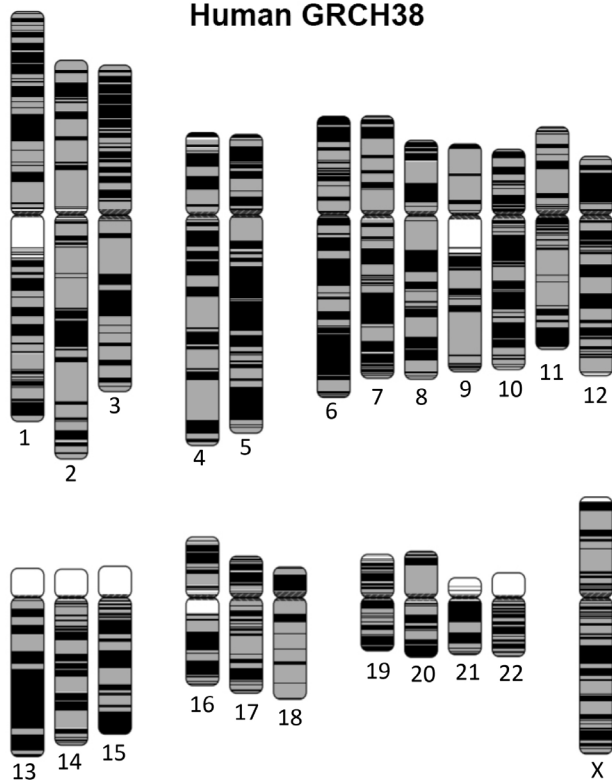
Brahman assembly



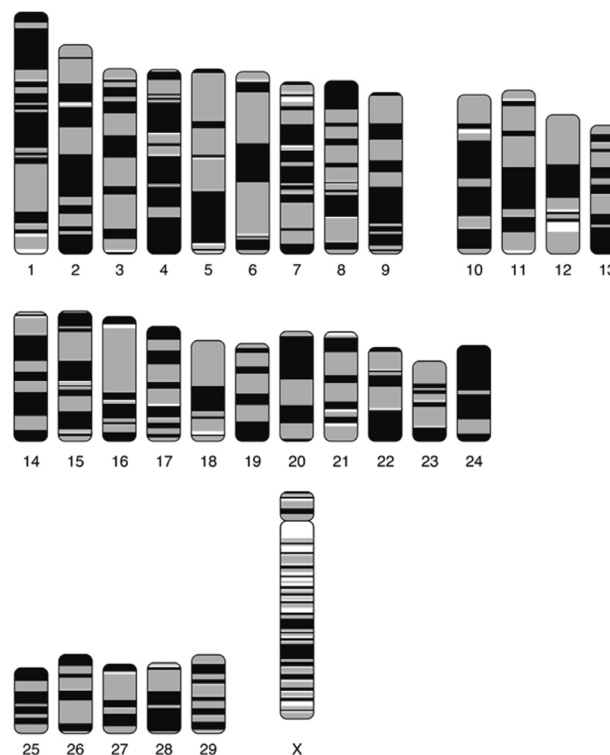
Comparison of assembly quality



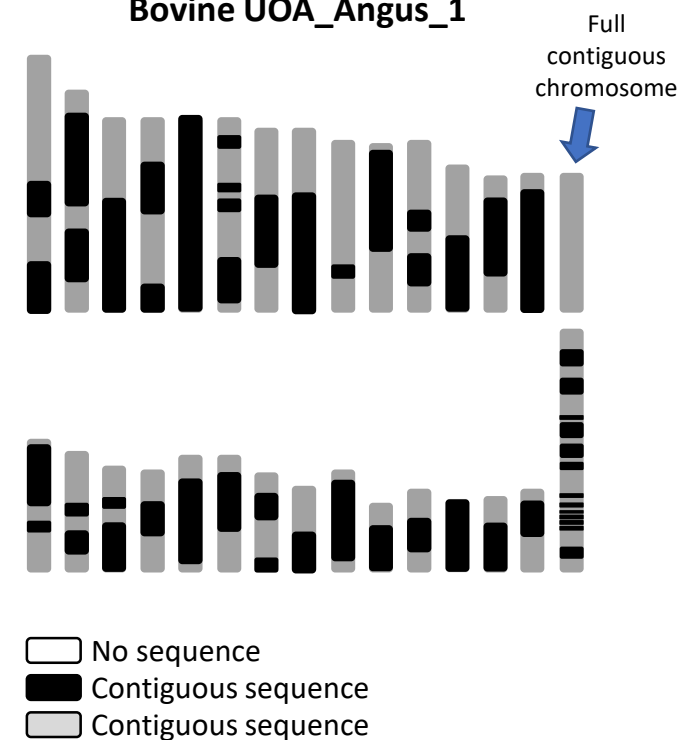
Human GRCH38



Bovine Hereford ARS-UCDv1.2



Bovine UOA_Angus_1



Interspecies crosses further improve genome assembly



Scottish Highland bull



Yak cow

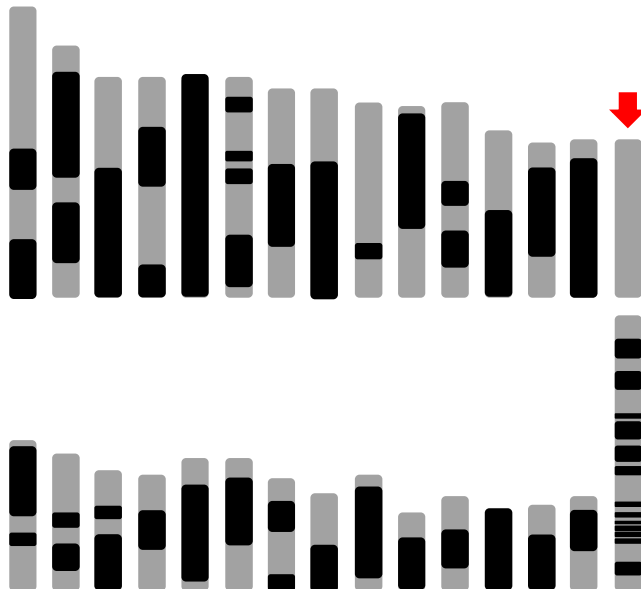


F_1 "Yaklander"

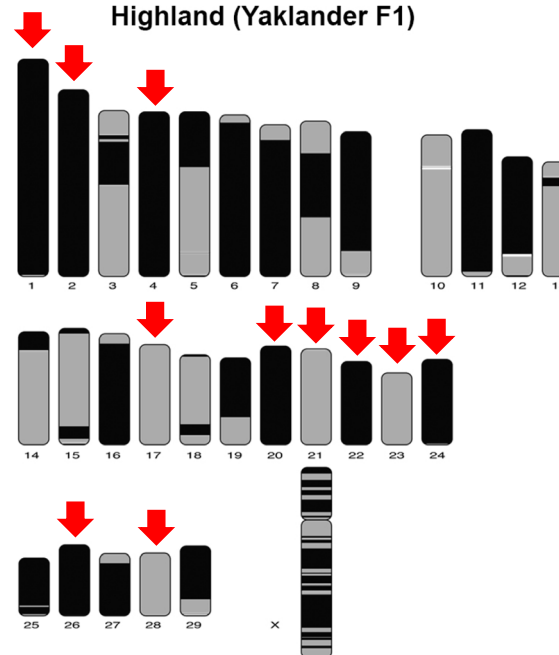
Comparison of assembly quality



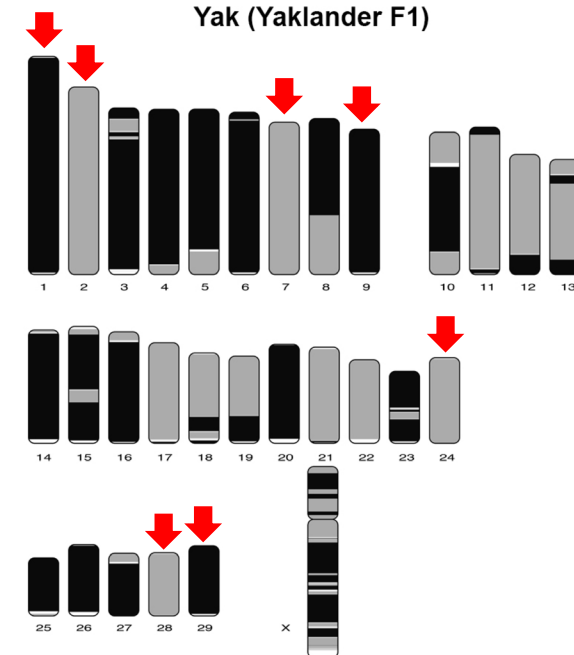
Bovine UOA_Angus_1



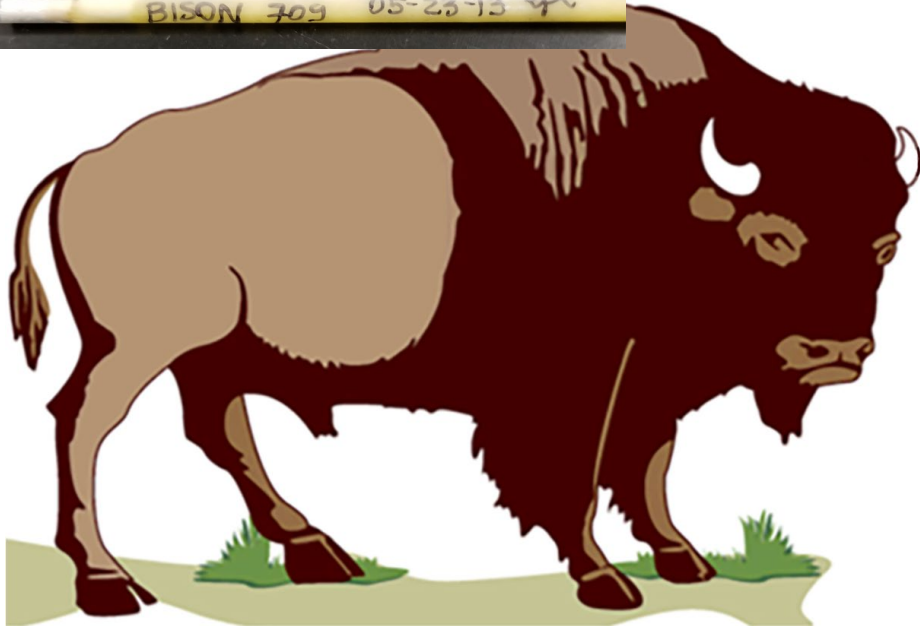
Highland (Yaklander F1)



Yak (Yaklander F1)



BiSimm Project



Plains bison bull

#709, 5/23/13 EPI



Simmental cow

BHR LADY SIEG C235E

Wade Shafer, American Simmental Assoc.

Fred Schuetze, Buzzard Hollow Ranch

Dr. Brad Stroud, Stroud Veterinary Embryo Services



Dr. Jennifer Barfield, CSU



Dr. Harvey Blackburn, NAGP, ARS



F₁ bison x Simmental fetus (120 days)

Drs. Tim Smith, Mike Heaton, Larry Kuehn, USMARC

Drs. Brian Vander Ley, Halden Clark, UNL-GPVEC

How it got done



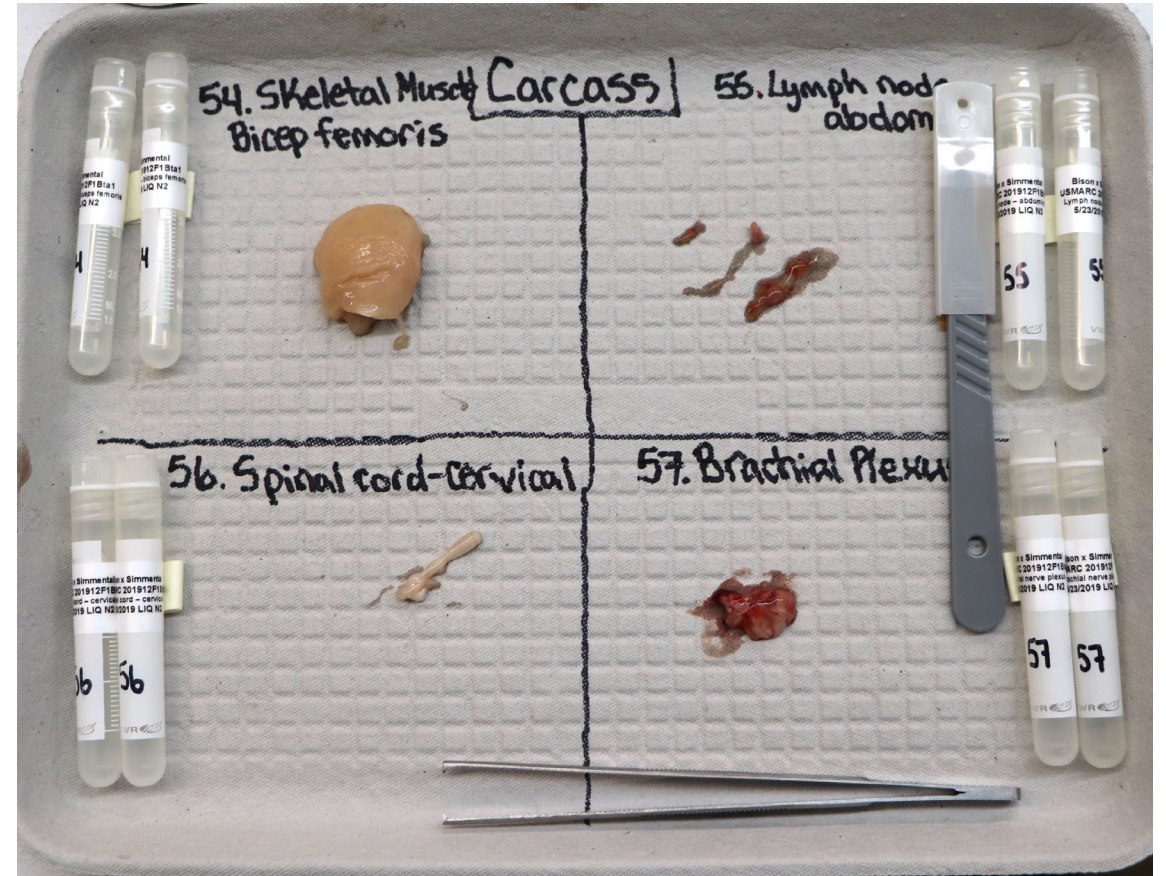
Recipient (left) with donor female C235E

Four veterinarians and a vet tech

May 23, 2019



Tissue dissection documentation



Multitasking



Processing tissue for liquid nitrogen

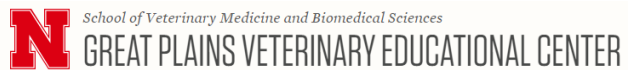


Attending to recipient, fetal dissection

All samples in liquid nitrogen within 37 minutes

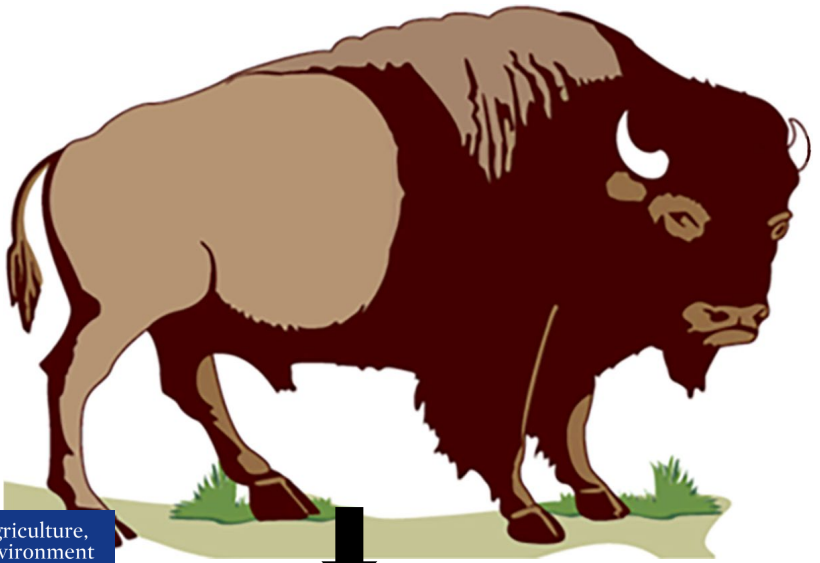


Collection team

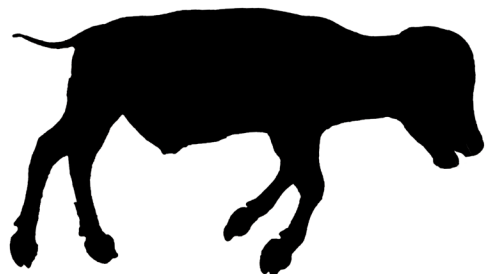


Left to right: Dr. Brad Stroud, Fred Schuetze, Dr. Halden Clark, Dr. Brian Vander Ley, Helen Smith, Dr. Adam Bassett, Brianna Harms, Michael Sadd, Jaden Carlson, and Madeline Pelster; inset: Mike Heaton.

What did we do in the lab?



X

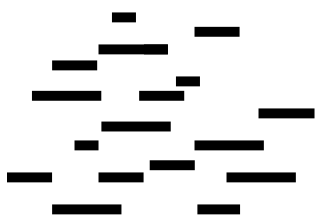


Sort

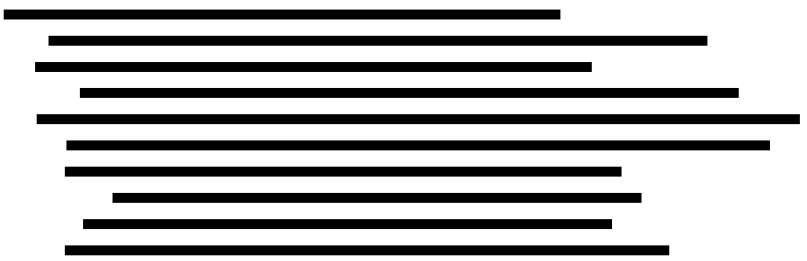
UK College of Agriculture,
Food and Environment



Dr. Ted Kalbfleisch



Short reads
< 1% cattle introgression



Short reads



When will the genomes be public?

As early as Spring 2020... if all goes well

Principle team handling genome assembly, analyses and manuscript development



Dr. Tim Smith, USMARC



Dr. Ben Rosen, ARS, Beltsville

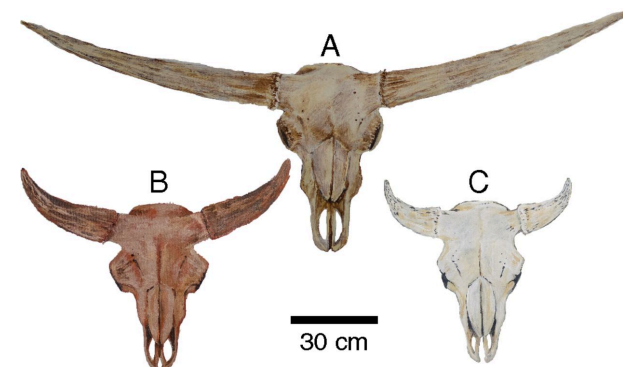


Dr. Derek Bickhart, ARS, Madison

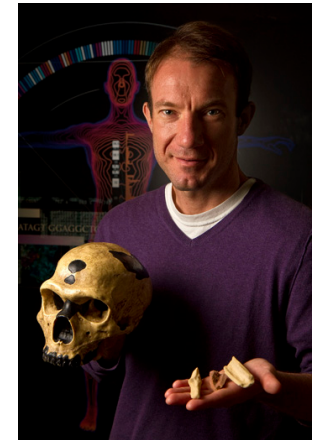
UC SANTA CRUZ



Dr. Beth Shapiro



Paleogenomics



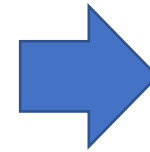
Dr. Ed Green



Jonas Oppenheimer

When finished, we will be able to align Simmental DNA sequence to a Simmental genome

- To see what we've been missing...



Simmental BHR LADY SIEG C235E



Conclusions

- Assembly of a Simmental reference genome is under way.



- The quality of the new Simmental genome is expected to equal or surpass that of existing genomes



- The best genomes produced the best results



