


## Gene Editing in Cattle: Recent developments and prospects


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**UCDAVIS**  
**ANIMAL SCIENCE**

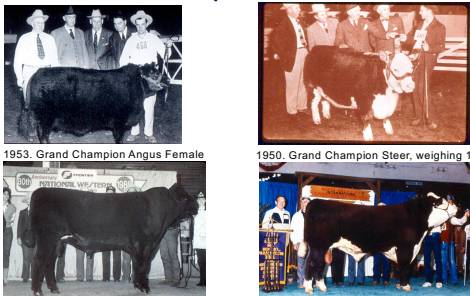
Email: [alvaneennaam@ucdavis.edu](mailto:alvaneennaam@ucdavis.edu)  
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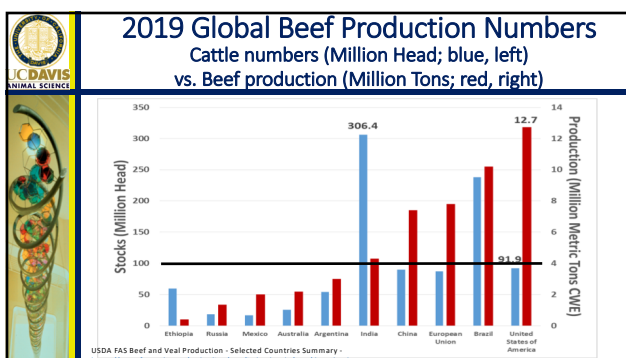
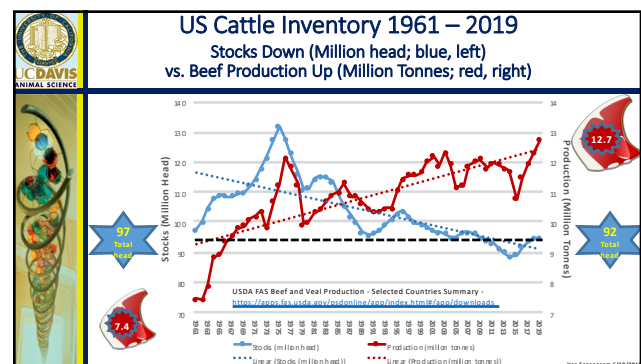
## Breeders have selected for desired changes to our food and companion animal populations



## 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

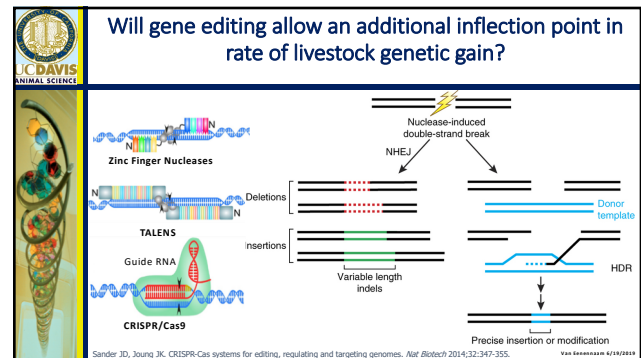
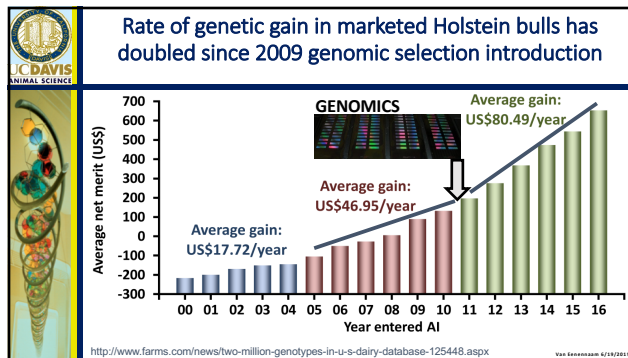


## The rate of genetic gain depends upon the four components of the breeders' equation

**Genetic change per year =**

$$\frac{(\text{Accuracy} \times \text{Intensity} \times \text{Genetic Variation})}{\text{Generation Interval}}$$

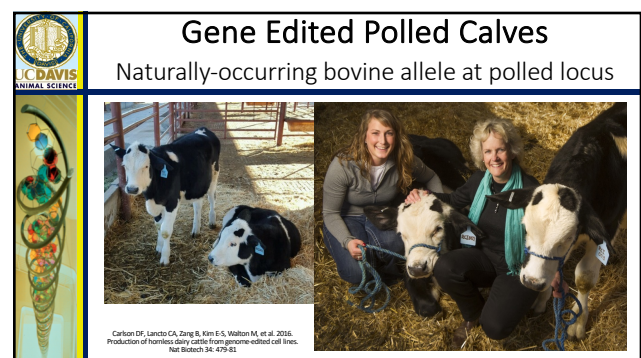
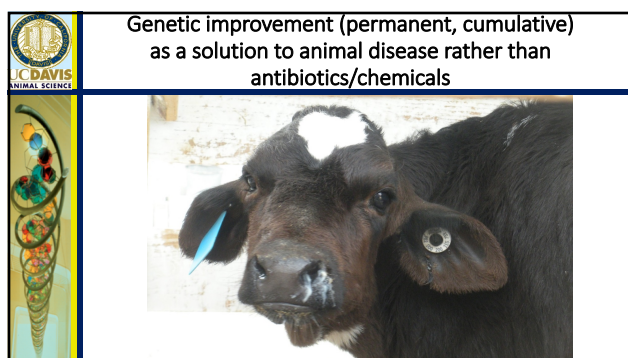
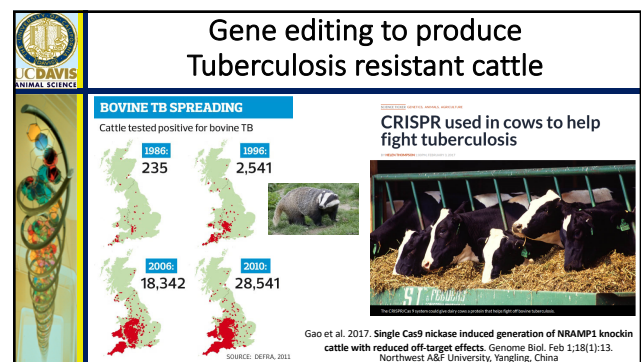
Accuracy = how certain we are about an animal's true genetic merit  
Intensity of selection = fraction of animals selected as parents  
Genetic variation = variation available in the population  
Generation interval = time between generations



### How might gene editing be used in cattle breeding programs?

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


Updated and modified from Van Eenennaam, A. I., 2017. *Current Opinion in Biotechnology*, 44:72-74.



dehorning  
YouTube: [https://youtu.be/-Qks\\_LMmodw](https://youtu.be/-Qks_LMmodw)



### Current polled dairy sires have inferior genetic merit

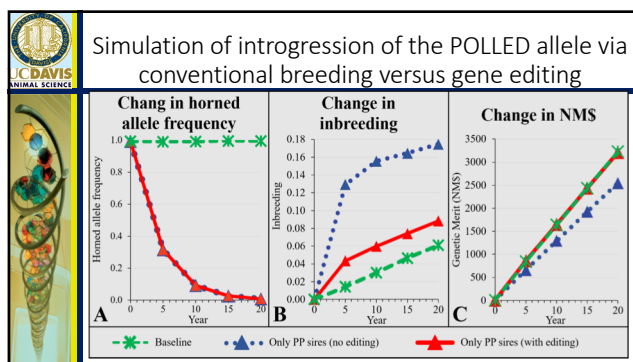


Average NMS of the top 50% of polled and horned Holstein and Jersey bulls registered with the NAAB in March 2018

Category	n	Average NMS
Polled (PP)	390	~400
Polled (Pp)	620	~650
Polled (Pp)	540	~550
Horned (pp)	717	~700
Horned (pp)	595	~500
Horned (pp)	794	~800

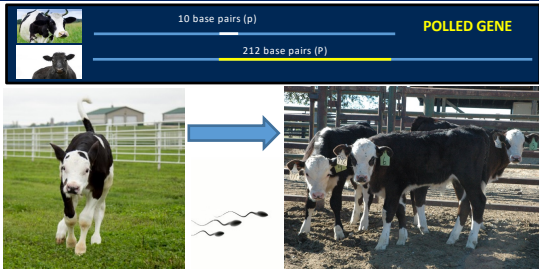
- ❖ Daughters of polled Holstein sires will earn less over their lifetimes
- ❖ Polled allele frequency is 0.0071
- ❖ Adding polled to selection indices is not effective
- ❖ If used exclusively polled sires would increase inbreeding & slow genetic gain

Mueller, M., J.B. Cole, T.S. Sonstegard, A.L. Van Eenennaam 2019. Comparison of gene editing versus conventional breeding to introgress the POLLED allele into the US dairy cattle population. *Journal of Dairy Science*. 102(5):4215-4226. <https://doi.org/10.3182/jds.2018.11879>



### Gene Edited Polled Calves

Naturally-occurring bovine allele at polled gene



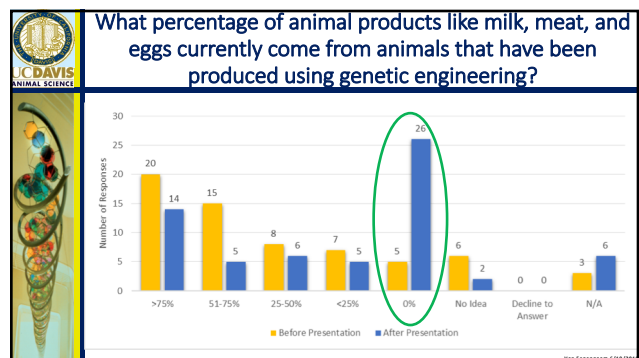
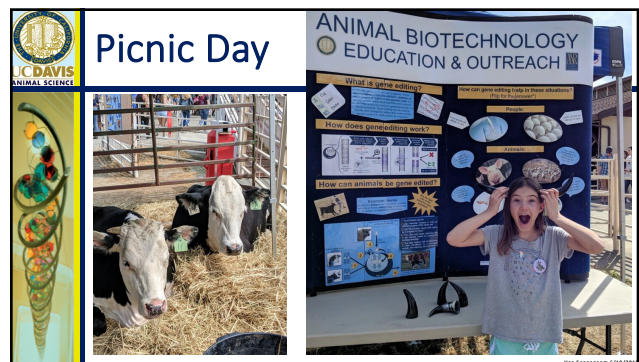
### Even a female cow has to get “made up” for a glamor shot!



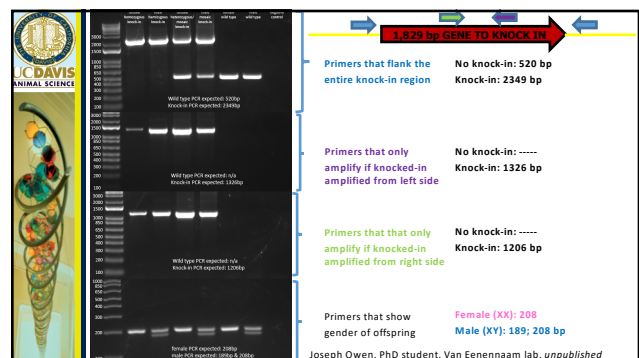
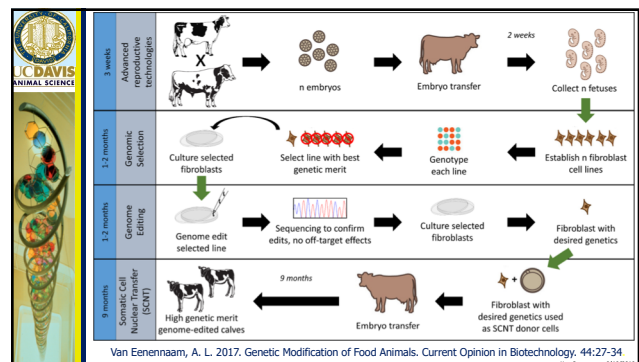
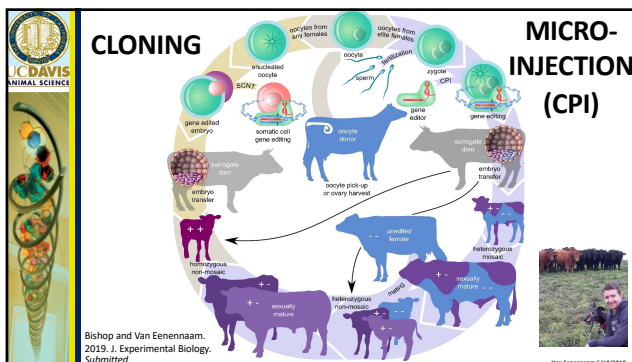
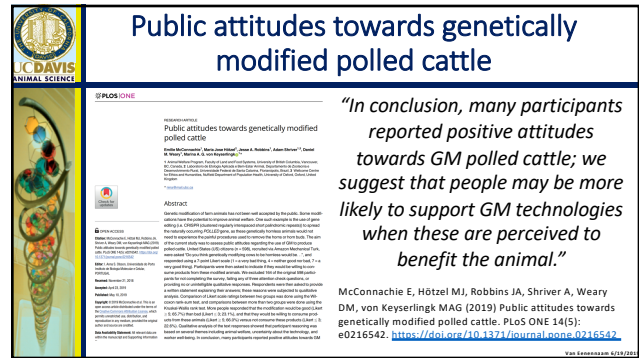
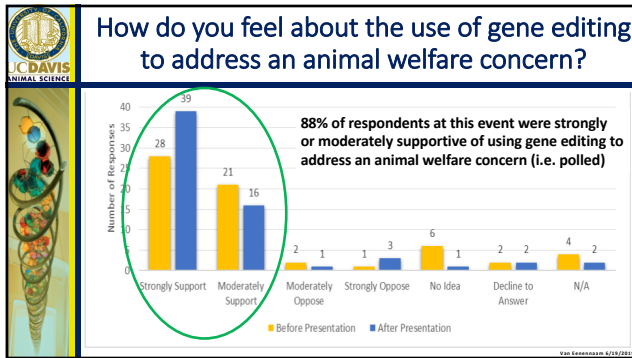
### Princess gets her 15 minutes of fame

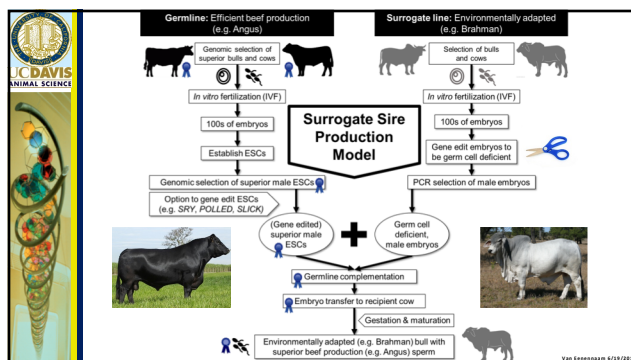
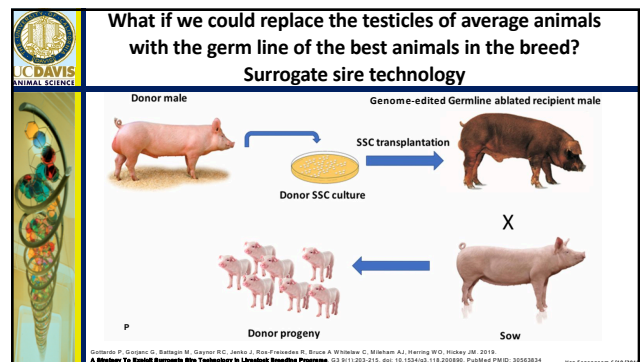
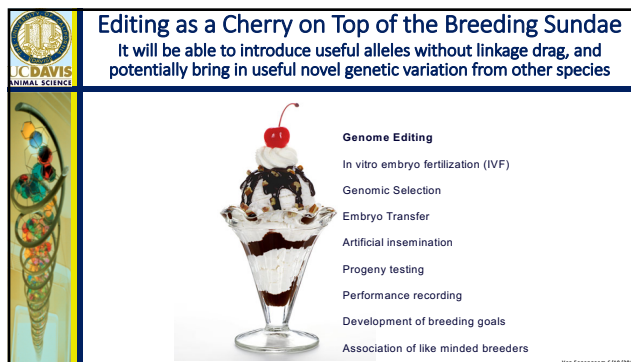
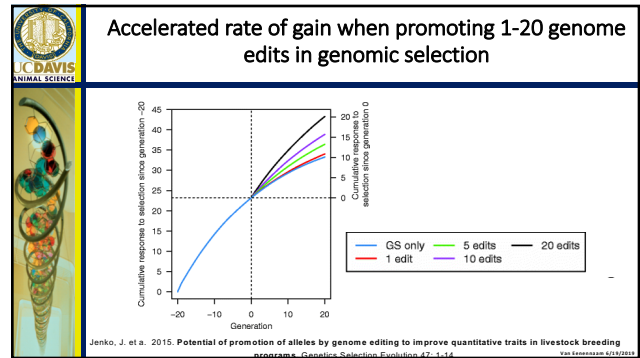
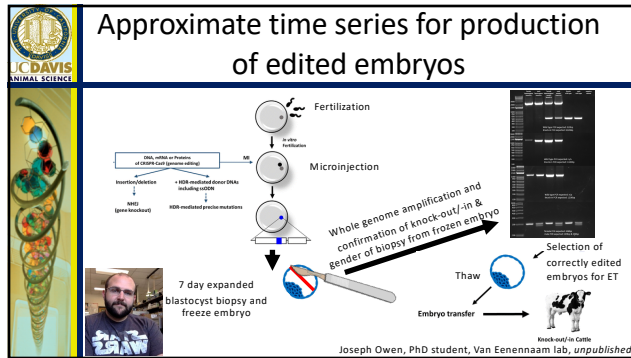













### No additional regulatory requirements if plants could otherwise have been developed through traditional breeding

The screenshot shows the USDA website with a headline: 'Secretary Perdue Issues USDA Statement on Plant Breeding Innovation'. The statement is dated March 28, 2018. It discusses the Secretary's statement on the U.S. Department of Agriculture's (USDA) oversight of plants produced through innovative new breeding techniques which include techniques called genome editing. Text at the bottom: 'Under its biotechnology regulations, USDA does not regulate or have any plans to regulate plants that could otherwise have been developed through traditional breeding techniques as long as they are not pests or developed using plant pests. This includes a set of new techniques that are increasingly being used by plant breeders to produce new plant varieties that are indistinguishable from those developed through traditional breeding methods. The newest of these methods, such as genome editing, expand traditional plant breeding tools because they can introduce new plant traits more quickly and precisely, potentially saving years or even decades in bringing needed new varieties to farmers.'


**January 18<sup>th</sup>, 2017 FDA draft guidance 187 considers all gene edited animals whose genomes have been “altered intentionally” to be drugs**



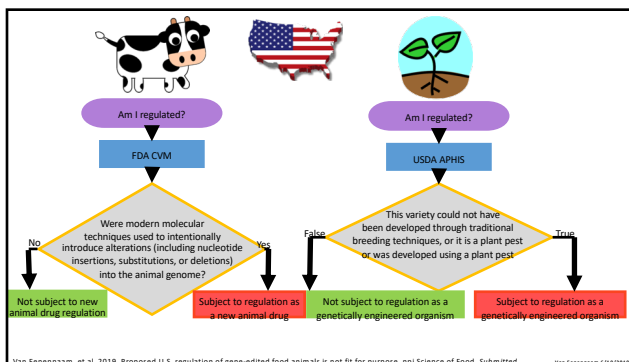
That does not sound very risk-based, more process-based

**> 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



**June 11, 2019 Presidential Executive Order**

**Executive Order on Modernizing the Regulatory Framework for Agricultural Biotechnology Products**

The Secretary of Agriculture (Secretary), the Administrator of the Environmental Protection Agency (Administrator), and the **Commissioner of Food and Drugs (Commissioner)**, to the extent consistent with law and the principles set forth in section 3 of this order, shall.....

**“use existing statutory authority, as appropriate, to exempt low-risk products of agricultural biotechnology from undue regulation.”**

**May 29, 2018 Canada has novel product based regulations**

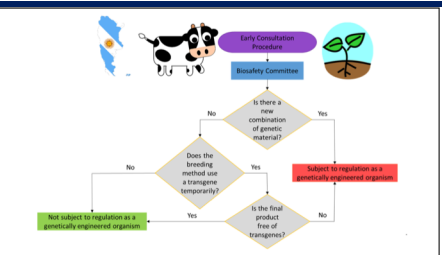
Eliminating dehorning in dairy cattle



recombinetics SEMEX

Recombinetics formed an alliance with Semex, a Canadian-based, farmer-owned cattle genetics organization to implement a precision breeding program to introduce hornless into elite dairy cattle genetics using genome editing

**2015 Argentina**




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graph TD
    A[Early Consultation Procedure] --> B[Biosafety Committee]
    B --> C{Is there a new combination of genetic material?}
    C -- No --> D{Does the breeding method use a transgene temporarily?}
    C -- Yes --> E[Subject to regulation as a genetically engineered organism]
    D -- No --> F[Not subject to regulation as a genetically engineered organism]
    D -- Yes --> G{Is the final product free of transgenes?}
    G -- No --> E
    G -- Yes --> F

```







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# 2019


## Australian Gene Technology Regulator






10 base pairs (p)

**POLLED GENE**



212 base pairs (P)

Template-guided, regulated, not deletions



Natural mutations

mutagenesis

SDN-1

no template

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+ template

■ not gene technology  
not GMOs, not regulated

■ gene technology,  
GMOs, regulated

SDN-2 and  
ODM









originator/cis

SDN-3

long template

Inserting  
transgenes

Via Sciencepark 579/579-2019

Would gene-edited polled Holsteins be subject to additional regulations in this country?			
Country		Additional Regulations?	Basis of trigger/regulation?
Argentina		No	Novel DNA sequence/transgene
Australia		Yes	Use of repair template
Brazil		No	Novel DNA sequence/transgene
Canada		No	Trait novelty (i.e. novel product risk)
European Union		Yes	Is a GMO if used a mutagenesis technique not in existence before 2001
Japan		No	No exogenous genes
New Zealand		Yes	Using of in vitro technique that modifies the genes/genetic material
United States		Yes	New Animal Drug

A composite image featuring a UC Davis Animal Science logo on the left, a large text overlay in the center, and a photograph of a laboratory on the right. The text overlay reads "Can't Stop the Feeding" and "YouTube: https://youtu.be/COMBIOBANHg". The photograph shows a laboratory with a poster titled "A. Van Eenennaam Laboratory" and "Pilot Identification and Training Required National Living and Environment in the Lab".

