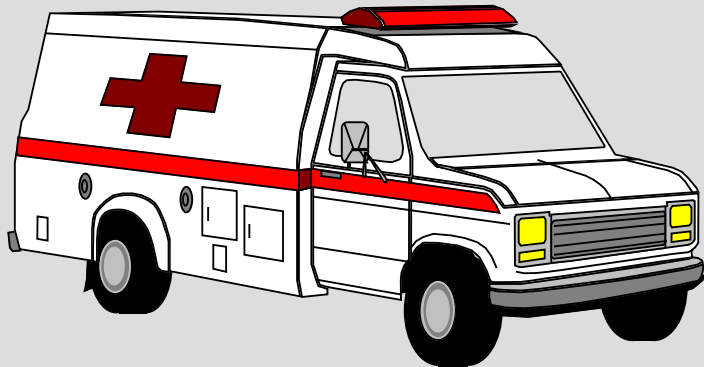
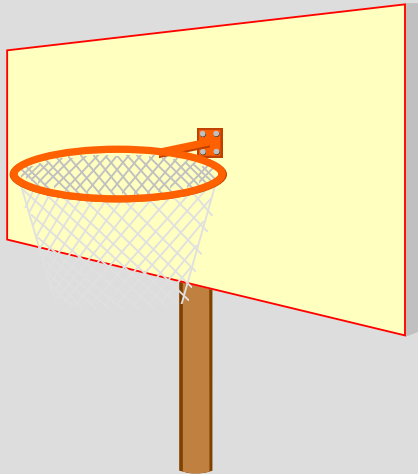
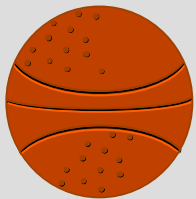




FACTORS INFLUENCING PEDIATRIC ASTHMA

4/5/17

COMMUNITY-BASED INITIATIVE



- **Chronic, intermittent**
- **Sometimes lifelong**
- **Often adequately controlled**
- **But often with serious morbidity/mortality**
- **Sometimes triggered by external environment**
- **Often worsened by tobacco smoke, air pollution**
- **More likely in families**

COMMUNITY-BASED INITIATIVE



- **Rae O'Leary, RRT, RN**
- **Respiratory Therapist**
- **Dr. James Wallace,**
 - **PEDS Pulmonologist, Sanford**
- **Developed intensive educational program for children with asthma**
- **Not a controlled trial**
- **Dr. Amy Elliot solicited ideas for CRCAIH**

CASE/CONTROL STUDY

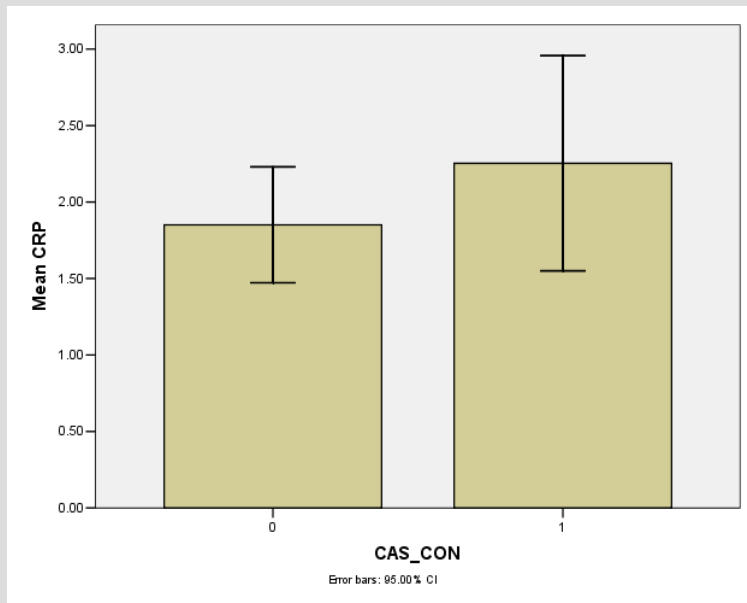


- 108 CHILDREN BETWEEN 6 AND 17 YO WITH A DIAGNOSIS OF ASTHMA
- EACH MATCHED WITH 2 CHILDREN WITHOUT ASTHMA
- AIR ENVIRONMENT TESTS
- BLOOD TESTS FOR ALLERGIES, INFLAMMATION
- DNA TESTING

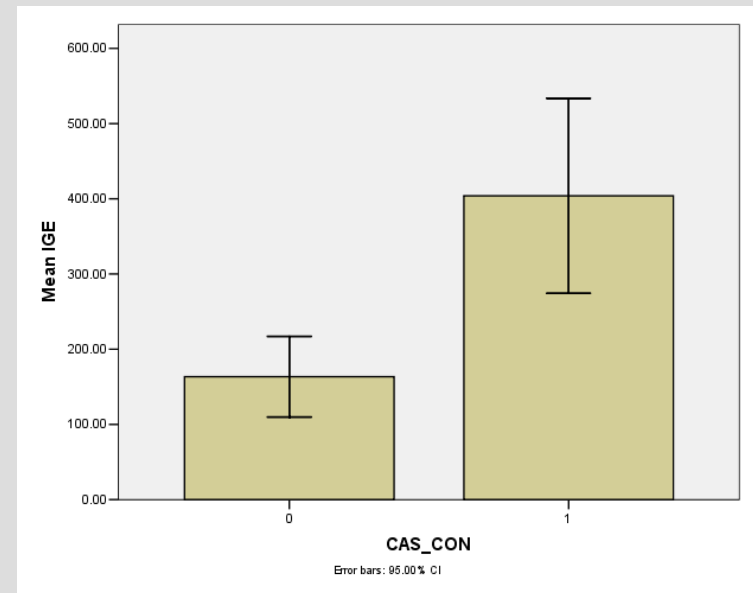
RANDOMIZED TRIAL

- **Intensive Education to improve control (BREATHE), N=104**
 - **Systematic follow-up for intervention arm, open access to asthma educator**
 - **“Usual Care” for control arm, written asthma education materials at enrollment**
 - **Outcome measure is Emergency Room visits related to asthma**
- **DSMB committee established (infrequent in tribal research)**
- **No statistically significant effect seen; but those with intensive education slightly less likely to visit ER.**
 - **Fewer ER visits among controls**
 - **Slightly fewer recruited and 4 declined RCT participation**

IMMUNE MEASURES



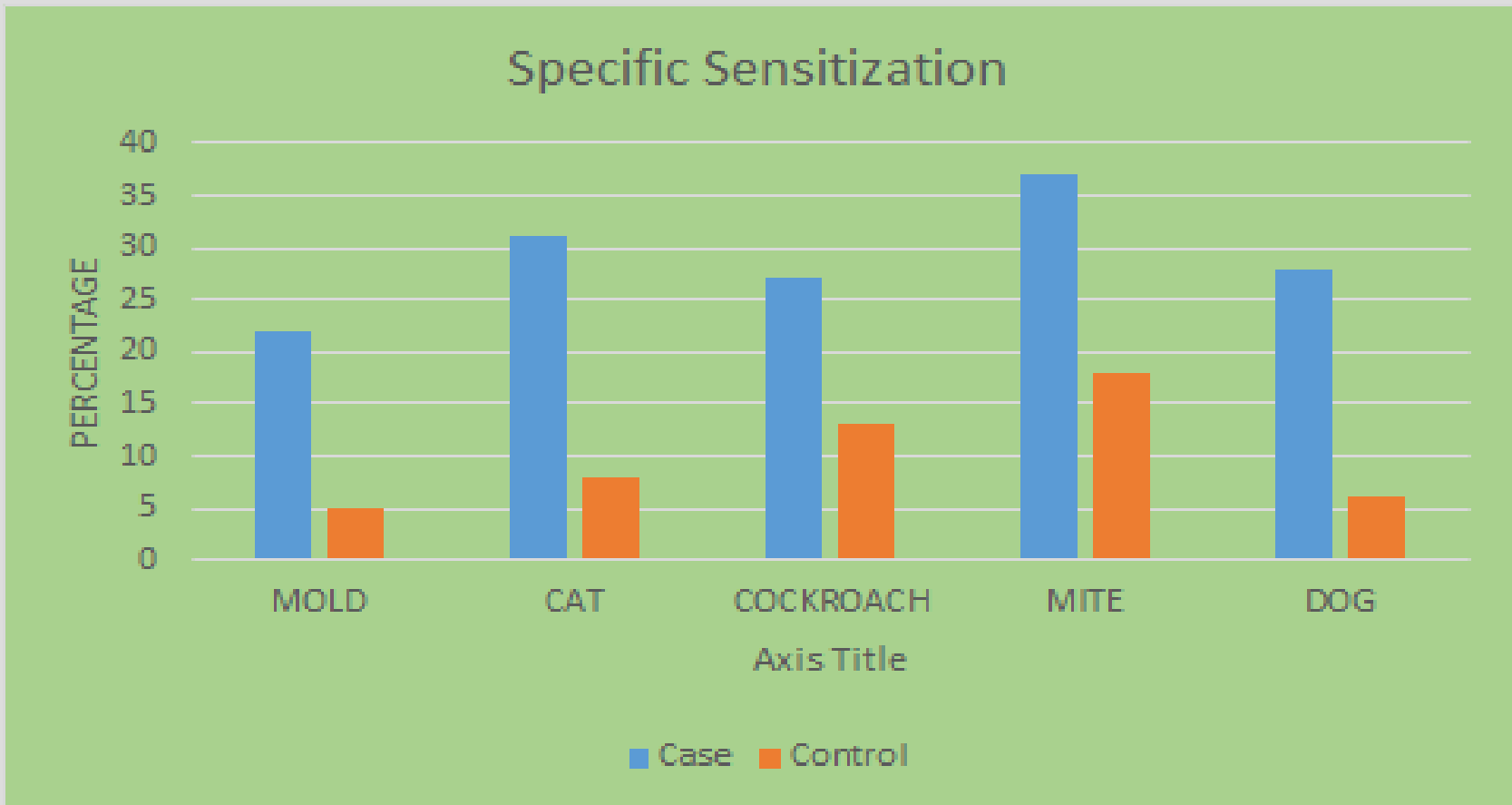
hsCRP



IgE

- Sensitivity to all tested individual allergens: mold, cat/dog, mite, cockroach was greater among cases compared with controls

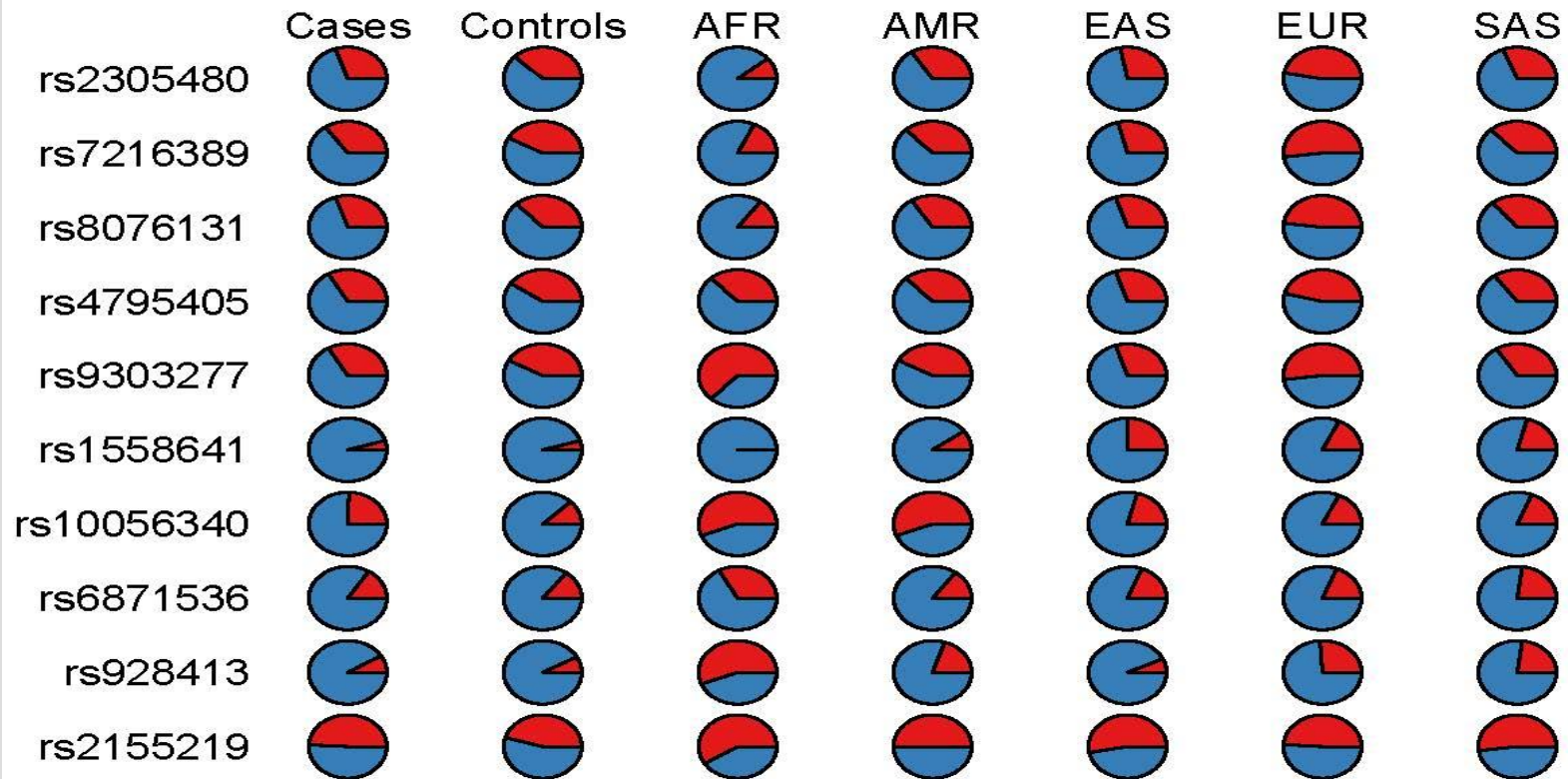
IMMUNE MEASURES



PREVALENCE OF GENETIC VARIANTS

dbSNP ID	Chromosome Band	Nearest Gene	Annotation	Alleles (major/minor)	Minor allele frequency*	95% CI	H-W p value
rs2305480	17q21	GSDMB	missense	G/A	35.0%	31.2 - 38.7	0.674
rs7216389	17q21	GSDMB	intronic	T/C	39.6%	35.8 – 43.4	0.872
rs8076131	17q21	ORMDL3	intronic	A/G	34.4%	30.7 – 38.2	0.512
rs4795405	17q21	LRRC3C	intronic	C/T	37.9%	34.1 – 41.7	0.792
rs9303277	17q21	IKZF3	intronic	C/T	39.0%	35.1 – 42.9	0.705
rs1558641	2q11.2	IL1R1	5' upstream	G/A	4.6%	3.0 – 6.3	0.088
rs10056340	5q21	SLC25A46-TSLP	intergenic	T/G	16.5%	13.6 – 19.3	0.317
rs6871536	5q31	RAD50	intronic	T/C	15.2%	12.4 – 18.0	0.596
rs928413	9q21	IL33	5' upstream	A/G	8.4%	6.2 – 10.5	0.541
rs2155219	11q13.4	EMSY-LRRC32	intergenic	G/T	47.3%	43.4 – 51.2	0.781

PREVALENCE OF GENETIC VARIANTS



EFFECTS OF GENETIC VARIANTS

Characteristic		OR	95% CI	p Value
Age		0.909	0.833 - 0.992	0.033
Body-mass index (BMI) Kg/m ²		3.219	1.204 - 8.610	0.020
> one specific antibody over detection limit		3.889	2.370 - 6.381	<0.001
Above 3 covariates plus genetic variants				
rs2305480, 17q21, A allele	Additive	0.635	0.434 - 0.927	0.019
rs7216389, 17q21, C allele	Additive	0.681	0.472 - 0.982	0.040
rs8076131, 17q21, G allele	Additive	0.668	0.459 - 0.971	0.035
rs4795405, 17q21, T allele	Additive	0.680	0.469 - 0.985	0.041
rs9303277, 17q21, T allele	Additive	0.648	0.447 - 0.940	0.022
rs1558641, 2q11.2, A allele	Additive	1.044	0.457 - 2.386	0.918
rs10056340, 5q21, G allele	Additive	2.020	1.283 - 3.180	0.002
rs6871536, 5q31, C allele	Additive	0.968	0.591 - 1.585	0.896
rs928413, 9q21, G allele	Additive	1.187	0.634 - 2.222	0.592
rs2155219, 11q13.4, T allele	Additive	1.206	0.842 - 1.729	0.306

GENES AT 5q21

1 SNP from 5q21 locus genotyped all participants

– rs10056340

• Intergenic, between *SLC25A46* and *TSLP*

– *SLC25A46*

• solute carrier family 25 member 46

• promotes mitochondrial fission and prevents hyperfilamentous mitochondria

– *TSLP*

• thymic stromal lymphopoietin

• promotes T helper, type 2 (TH2) response seen in asthma and other inflammatory diseases

GENES AT 17q21

- 5 SNPs from 17q21 locus genotyped all participants
 - rs7216389, *GSDMB* gene, “gasdermin B”, intronic
 - Regulation of apoptosis in epithelial cells
 - rs2305480, *GSDMB* gene, coding, missense
 - rs8076131, *ORMDL3* gene, intronic
 - “sphingolipid biosynthesis regulator 3”
 - possible role in Ca⁺⁺ signaling, lymphocyte activation
 - rs4795405, *LRRC3C* gene, intronic
 - immune modulator
 - rs9303277, *IKZF3* gene, intronic
 - transcription factor regulating lymphocyte development

Calcium-Sensing Receptor

BBC Sign in News Sport Weather

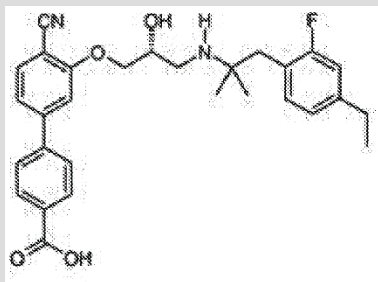
NEWS

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Asthma breakthrough treatment hope by Cardiff University experts



CaSR gene on chromosome 3, not tested in present study
Calcilytics: e.g. NPS89636, used in osteoporosis treatment

Sci Transl Med 22 April 2015:
Vol. 7, Issue 284, p. 284ra60
Sci. Transl. Med. DOI: 10.1126/scitranslmed.aaa0282

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RESEARCH ARTICLE

ASTHMA

Calcium-sensing receptor antagonists abrogate airway hyperresponsiveness and inflammation in allergic asthma

Polina L. Yarova¹, Alecia L. Stewart^{2,*}, Venkatachalem Sathish^{2,*}, Rodney D. Britt Jr.^{2,*},

Michael A. Thompson^{2,*}, Alexander P. P. Lowe^{4,*}, Michelle Freeman², Bharathi Aravamudan², Hirohito Kita³, Sarah C. Brennan¹, Martin Schepelmann¹, Thomas Davies¹, Sun Yung¹, Zakky Cholisoh⁴, Emma J. Kidd⁴, William R. Ford⁴, Kenneth J. Broadley⁴, Katja Rietdorf⁵, Wenhan Chang⁶, Mohd E. Bin Khayat⁷, Donald T. Ward⁷, Christopher J. Corrigan⁸, Jeremy P. T. Ward⁸, Paul J. Kemp¹, Christina M. Pabelick², Y. S. Prakash^{2,†} and Daniela Riccardi^{1,†}

TRANSLATIONAL EFFORTS



- 3/1/16, NIMHD approves Joe Yracheta's training grant for ancillary study of immune factors among FIPA participants
- leveraging:
 - Joe's extensive knowledge of genetics
 - MBIRI's MagPix instrument
 - repository of FIPA samples
- **Congratulations Joe!**
- **Thanks NIMHD and CRCAIH!**

TRANSLATIONAL EFFORTS

- **Completed or in process, 2017**
 - **PRESENTATION OF FINDINGS TO THE LOCAL MEDICAL STAFF, 9/22/15**
 - **REVIEW AND APPROVAL OF MANUSCRIPTS BY TRIBAL GOVERNMENT**
 - **PRESENTATION AT AAIP, 7/31/15**
 - **PARTICIPATION IN CRST RESEARCH CONF, 4/10/15, 3/24/16**
 - **ENGAGEMENT WITH INMED, HIGH SCHOOL AND SUMMER ENRICHMENT PROGRAMS**
 - **STUDENT POSTER PRESENTATIONS:**
 - **INBRE, Grand Forks, ND, 10/23/15**
 - **CCCC, Fort Totten, ND, 4/1/16**

TRANSLATIONAL EFFORTS

- **Genetics Demonstrations at tribal colleges and schools**
 - **Willing students collect their own DNA**
 - **Test their ability to taste a specific substance (PTC)**
 - **Test their DNA for the variant that allows tasting of PTC**
 - **Expected correlation between genotype and phenotype?**
 - **Ethics and potential career/business opportunities in genetics**
 - **Pre and Post survey to evaluate attitude and knowledge about genetics (^ knowledge post test)**
- **One tribal college and ~20 INMED students in 2014**
- **INMED, Duluth CAIMH, Sanford Research, TMCC, 2015**
 - **57 students participated**
- **NDSU, 2016, SURP program, 6 students**

PUBLICATIONS

Best et al. *BMC Pulmonary Medicine* (2016) 16:93
DOI 10.1186/s12890-016-0257-6

BMC Pulmonary Medicine

RESEARCH ARTICLE

Open Access



Humoral immune factors and asthma among American Indian children: a case-control study

Lyle G. Best^{1,2,3*}, Rae A. O'Leary¹, Marcia A. O'Leary¹ and Joseph M. Yracheta¹

- **Immune measures**
 - **Best LG, O'Leary RA, O'Leary MA, Yracheta JM. Humoral immune factors and asthma among American Indian children. BMC Pulm Med. 2016;16:93.**
- **Genetic effects**
 - **under review at Annals of allergy, Asthma and Immunology**
 - **Lead: Best, LG**
- **Indoor air quality**
 - **Lead: Yracheta, Joseph**
- **Pulmonary function testing**
 - **Lead: O'Leary, Rae**
- **Social determinants of health**
 - **Lead: Kinghorn, Breanna**
- **Recruitment and Retention**
 - **Lead: O'Leary, Rae**

Annals
of Allergy, Asthma & Immunology

OFFICIAL PUBLICATION OF THE AMERICAN COLLEGE OF ALLERGY, ASTHMA & IMMUNOLOGY



Articles & Issues ▾ Collections ▾ News Archive Allergen of the Month

STUDENT RESEARCHERS



- Obtain informed consent from participants
- Collect samples, analyze DNA
- Research literature, manuscript prep
- Teach other students about their experience
- Total of 37 SRAs involved with program to date
 - 21 Completing BS or greater in nursing, social work, secondary science education, physical therapy
 - 1 Physician Assistant
 - 1 Medical School Student, 2nd YEAR
- First lab tech, 2004, pending PhD in Epidemiology at U. Minn

NEW INITIATIVES



- **Minority Supplement to Strong Heart Study (Dakota Center) for Kaytlin Lawrence**
 - **2nd year Medical Lab Tech at University of Mary**
 - **Previously worked as summer intern for MBIRI**
 - **extending recruitment of SHS participants to investigate pre-eclampsia**
 - **Obtaining additional instrumentation (thermocycler) through SPHERE, Precision Medicine grant at Stanford University**

REAL TIME ANALYSIS



- “Regular” PCR = run reaction, then analyze to see how much DNA was produced
- “Real-Time” PCR = run reaction and watch in “Real Time” how much DNA is produced cycle by cycle

NETWORKING



- Laboratory and student research assistants at Turtle Mountain Community College
- Univ. North Dakota, INBRE
- Sanford Research, CRCAIH
- Stanford University, SAIL Study
- Stanford University, Precision Medicine (SPHERE) grant
- Strong Heart Study, NHLBI
- YouTube “Red Talks”, NCAI

Acknowledgements

- **Collaborators:**
 - Ms Rae O’Leary, Mr. Joe Yracheta, Kendra Enright, Terilynn Half Red
- **Cheyenne River Sioux Tribe**
- **Cheyenne River Sioux Tribal Health Department**
- **Turtle Mountain Community College**
- **Indian Health Service, especially the Eagle Butte IHS Hospital and Staff**
- **The CRCAIH grant and Sanford Research**
- **The North Dakota INBRE program**

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