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Short Title: Genetic Research Involving Navajo People

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Abstract

To date, some genetic studies offer medical benefits, but lack a clear pathway to benefit for people from underrepresented backgrounds. Historically Indigenous people, including the Diné (Navajo people), have raised concerns about the lack of benefits, misuse of DNA samples, lack of consultation, and ignoring cultural and traditional ways of knowing. Shortly after the Navajo Nation Human Research Review Board was established in 1996, the Navajo Nation recognized growing concerns about genetic research and established a moratorium on human genetic research studies in 2002. The moratorium effectively has protected their citizens from potential genetic research harms. Despite the placement of the moratorium, some genetic research studies have continued using blood and DNA samples from Navajo people. In order to understand the history of genetic research involving Navajo people, we conducted a literature review of 79 genetic or genetic-related research publications that involved Navajo people from the years 1925 to 2018. In this review, we divided the genetic research studies into the following general classifications: a) bacteria or virus genetics studies, b) blood and human leukocyte antigen, c) complex diseases, d) forensics, e) hereditary diseases, and f) population genetics and migration. We evaluated the methods for each study, described the number of Navajo individuals included in each study, recorded the academic or tribal approval statements, and noted whether the study considered Diné cultural values. Several studies focused on Severe Combined Immunodeficiency

Disease, population history, neuropathy, albinism, eye and skin disorders that affect Navajo people. We found genetic research publications involving Navajo people spanning over the course of 93 years. To our knowledge, no known literature reviews have examined the history of genetic research in the Navajo community. In our Discussion, we contextualize Diné ways of knowing related to genetics and health with Western scientific concepts to acknowledge the complex philosophy and belief system that guides Diné people and recognizes Indigenous science. We encourage researchers consider cultural perspectives and traditional knowledge that has the potential to create stronger conclusions and better informed, ethical, and respectful science.

While Indigenous people have been subjects of genetic research for decades, the number of research studies involving them has remained relatively low. Since the first human genome was sequenced in 2003, the field of genetics has rapidly improved its sequencing technology and increased access, allowing more researchers and clinicians to address fundamental questions that may lead to individualized patient healthcare (National Institutes of Health, 2015; Schmutz et al., 2004; Wetterstrand, 2019). In genomic medicine, scientists and clinicians are able to use these improved tools to study the role of multiple genetic factors, acting together with the environment to understand various hereditary and complex diseases. However, the majority of genetic studies have largely been conducted in people of European descent thus potentially benefiting them and excluding other populations such as Indigenous people (Mills & Rahal, 2019; Popejoy & Fullerton, 2016). Indigenous scientists are beginning to integrate traditional knowledge with important research questions to address inequities in genetic research.

Indigenous people, the original caretakers of a given land, possess a wealth of inherent knowledge of heredity and genetics. Some Indigenous groups, such as the Navajo, have used such knowledge from time immemorial to recognize kinship and familial relationships, to interact with their environment, and use complex breeding practices with livestock (e.g., sheep) and crops to yield favorable physical characteristics (Bousselot et al., 2017; Sponenberg & Taylor, 2009). While these concepts are known collectively as "genetics" in contemporary Western science, much of *iiná bitł'ool* (DNA, or "strands of life") concepts have been shared through lived experiences, conveyed orally through storytelling, and have ultimately been woven into the cultural and traditional epistemology of the Navajo people for generations. The Navajo Nation is the second largest tribe in the United States (US) with over 350,000 enrolled citizens and has the largest tribal land base spanning the states of Arizona (AZ), Utah, and New Mexico

(NM) covering over 27,000 square miles. *Diné* (The People, also known as Navajo), as they refer to themselves, have lived on their homelands for generations, and many still live within the boundaries of the four sacred mountains located in AZ, NM, and Colorado.

Indigenous populations have been reticent to join many types of research studies for various reasons related to historical research harms such as misuse of DNA samples, disrespecting Indigenous cultural/traditional ways of knowing, and other ethical concerns (American Journal of Medical Genetics, 2010; Arbour & Cook, 2006; Beans et al., 2019; Claw et al., 2018; Drabiak, 2010; Garrison et al., 2019). In order to further protect their tribal citizens, the Navajo Nation established nationally recognized research regulations in 1996 requiring all human subject research studies conducted within the jurisdiction of the Navajo Nation be reviewed and approved by the Navajo Nation Human Research Review Board (NNHRRB) while simultaneously abiding by US research regulations including the US Department of Health, Education, and Welfare regulations for the protection of human subjects in 1974 and the "Common Rule" in 1991 with recent its updates (Brugge & Missaghian, 2006; Department of Health and Human Services, 2005, 2017; Navajo Nation Human Research Review Board, 2009; United States National Commission for the Protection of Human Subjects of Biomedical Behavioral Research, 1978). Prior to the Navajo Research Act of 1996, medical research on Navajo lands was reviewed and approved by the Indian Health Services (IHS) Navajo Area Institutional Review Board (IRB). Thereafter, the functions of IHS IRB were assumed by the NNHRRB, in addition to all other human subjects research (Brugge & Missaghian, 2006).The purpose of the NNHRRB has been to enhance and promote ethical and beneficial research for the Diné people, and to nurture a culturally respectful relationship between Diné and Western

scientific knowledge in approved research (Navajo Nation Human Research Review Board, 2009).

In April 2002, the Navajo Nation asserted its sovereign authority to limit genetic research when the Navajo Nation Health and Human Services Committee (HHSC) approved a "moratorium on genetic research studies conducted within the jurisdiction of the Navajo Nation until such time that a Navajo Nation Human Research Code has been amended by the Navajo Nation Council" (Navajo Nation, 2002). This suspension of genetic research applies to all studies involving tribal members who live on the Navajo Nation. The moratorium came from a collective decision resulting from lengthy consultations with the Navajo Nation's HHSC, tribal leaders, traditional healers, and Navajo people with medical and scientific training (Brown, 2002). A common concern among these groups was that the Navajo Nation lacked an appropriate policy or set of guidelines to regulate genetic research protocols that might be culturally discordant with traditional Diné values (Brown, 2002; National Congress of American Indians, 2012). For over 18 years, the moratorium did in fact deter genetic research projects from being conducted on the Navajo Nation and also served to protect the Navajo people from potential genetic research harms.

To our knowledge, no known comprehensive reviews have examined the history of genetic research in the Navajo community to date. Here, we conducted a literature review of 79 genetic research articles that include Navajo people as research subjects. We further discuss Western scientific concepts in concert with Navajo cultural and traditional examples of genetic knowledge that reflect Diné ways of knowing (epistemology), a complex philosophy and belief system, that guides Diné people and acknowledges Indigenous science.

Methods

We conducted an online literature search using PubMed and Google Scholar applying the keywords: “Navajo,” “Navaho,” “Diné,” “Dine,” “Dene,” “Athabaskan,” “Athapaskan,” “Southwest tribe.” “Arizona tribe,” “American Indian,” “genetics,” “genomics,” “disease,” and “research.” The word “Athabaskan” (also known as “Dene” or “Na-Dene”) refers to a large language family that includes Northern, Pacific Coast, and Southern Indigenous groups and was included in the search because Navajo people are sometimes referred to as “Southern Athabaskans or Athapaskans” in the literature. In addition to our online search, a dataset of Navajo genetic, health, and public health related articles were curated by Dr. Bonnie Duran for the Native Health Database retained at the University of New Mexico (Native Health Database, 2018). This dataset included 300 articles published from the years 1862-1969.

Our three inclusion criteria were: original research published in English before December 2018 (date of search), involved the use of genetics and family pedigrees, and studied Navajo human and non-human human-derived biospecimens. News, comments, clinical reports, and reviews were excluded from the results but are cited as additional references when appropriate. We were not able to confirm tribal enrollment status of individuals; therefore, we only reported the number of Navajo individuals if the authors clearly labeled samples or data as ‘Navajo’ or ‘Diné’ and any other spelling versions mentioned above. Original studies using secondary data or using shared Navajo samples were included. Figure 1 depicts a flowchart of the inclusion and exclusion criteria mentioned above.

During our analysis of the full-text articles, we extracted the following information from each publication: publication year, publication journal, disease associated gene(s) or chromosomal region sequenced, mode of inheritance, sequencing technology or methods used,

number of Navajo people included in study, type of IRB oversight, and noted secondary use of data or samples. We categorized all articles by general fields of study. Our review also discusses cultural and traditional knowledge of genetics or genetic-related diseases which were informed by our elders or own experiences living in the Navajo community.

The authors are involved in health research and/or research regulation on the Navajo Nation and most are enrolled members of the Navajo Nation. Due to the sensitive nature of our review article topic, we submitted our manuscript to the NNHRRB for pre-review and obtained permission on October 23, 2019 to proceed with publication.

Results

Of the 408 studies identified via online search or the Native Health Database, 79 studies of genetic or genetic-related research met our inclusion criteria (Figure 1). Broadly, we classified articles by their general field: bacteria or virus genetics (12 studies), blood and HLA (12 studies), complex diseases (7 studies), forensics (4 studies), hereditary diseases (25 studies), and population genetics and migration (19 studies).

Table 1 reports these six general fields, specific disorders within each group, and the total number of Navajo individuals in each study. In total, 13,355 Navajo people were included in published research studies related to genetics over the past 93 years. Most individuals (n=8,540) were involved in studies in the hereditary disease category and the fewest (n=69) individuals were in the complex disease category.

Figure 2 depicts a timeline (1925-2018) by publication year for the 79 studies included in our analysis. Interestingly, bacteria/virus studies were more prevalent after the moratorium was established. Before the advent of sequencing technology, most genetic studies used phenotypical

observations, such as blood or HLA-typing, and this trend is reflected in our data with these studies primarily occurring before the 1990s. The majority of studies (hereditary disease, complex disease, forensics, and population genetics and migration) were published from 1990 to 2000 (48 studies), when sequencing technology improved tremendously and just before the Navajo Nation enacted the genetic research moratorium.

Overall, of the 79 studies, 45 studies (57%) did not cite review board approval, whereas 10 studies (13%) mentioned both tribal and academic IRB approval, 17 studies (22%) obtained only academic IRB approval, and 7 studies (9%) only acknowledged tribal entities and did not mention other review board approvals (Supplementary Table 1). Publications before 1991 are distinctive because ethical, journal, and reporting standards drastically changed after 1991 because of the establishment of the Common Rule. Before 1991, human subject approval was not routinely sought or stated in publications. We found 21 studies published in or before 1991; of those 3 studies thanked tribal entities and 4 studies mentioned academic IRB approval. Moreover, 36 (46%) of 79 studies were published in or before 1996 when the NNHRRB was established; of those studies, 5 of the 36 studies stated that they obtained academic IRB approval only. In addition, 25 (32%) of 79 studies were published after the 2002 moratorium, of which 7 studies involved bacterial/viral genetics and 18 studies involved human genetics. Of the 25 studies, 8 studies did not cite review board approval, whereas 7 studies mentioned both tribal and academic IRB approval, and 10 studies obtained only academic IRB approval. Finally, 30 (38%) of 79 studies collected samples on the Navajo Nation, 16 studies (20%) collected samples off the Navajo Nation (e.g., urban areas), 14 studies (18%) collected samples both on and off the Navajo Nation, and 19 studies (24%) did not mention where samples were collected. This brings into question the jurisdictional reach of the moratorium and the effects of researchers conducting

research away from tribal oversight. A total of 19 studies indicated they used secondary data from previously published datasets or sample collections.

Bacteria or Virus Genetics

Genetic material from bacteria and viruses is distinct from human DNA. Yet, bacteria inhabit almost every tissue of the human body and microbes outnumber human cells by 10:1. Twelve microbiology studies used genetic techniques to assess the epidemiology of the diseases or the diversity of the bacteria or virus strains that are known to affect humans. These studies extracted and studied bacterial or viral DNA from samples acquired from human subjects.

Of the twelve studies, three studies focused on T-cell lymphotropic virus Type II or T-cell leukemia virus Type II (HTLV-2) (Biggar et al., 1996; Hjelle et al., 1993; Switzer et al., 1995), two on *Pneumococcal* isolates (Scott et al., 2012a; Scott et al., 2012b), two on *Streptococcus pneumoniae* (Azarian et al., 2018; Lipsitch et al., 2007), two on rotavirus (RV) (Grant et al., 2011; Grant et al., 2012), two on the *Human polyomavirus 2*, formerly called the JC virus (Agostini et al., 1997; Fernandez-Cobo et al., 2002), and one on *Haemophilus influenzae* Type A and Type B (Millar et al., 2005). The majority of these infectious microbes have high prevalence on the Navajo Nation. For example, *H. influenzae* is a leading cause of bacterial meningitis in children and HTLV-2 can be spread by blood transfusions, sexual contact, and sharing of needles. These studies were published from years 1993-2018.

In particular, we would like to highlight the studies that involved analysis of *Haemophilus influenzae* and *Streptococcus pneumoniae* strains because of the researcher's inclusive and collaborative nature (Lipsitch et al., 2007; Millar et al., 2005). These studies occurred from 2005-2018 and used genetic methods to diagnose and type the bacterium. These

studies all mention obtaining NNHRRB and academic IRB approval and also include Navajo researchers as co-authors. Studies involving bacteria and viruses were included in this review because of their symbiotic relationship with the human body.

Blood and Human Leukocyte Antigen (HLA)

Blood samples provide clinicians and researchers with metabolic, immunologic, and genetic (DNA, RNA, and proteins) information that is easily obtainable and has a long storage life. Four studies related to blood type frequencies were conducted in the early half of the 19th century. Some of the earliest studies used blood type frequencies to understand why populations differ from each other (Corcoran & Rabin, 1961; Nigg, 1925). These studies examined blood types in 457 Navajo children from two communities in Arizona (Fort Defiance and St. Michaels) (Nigg, 1925) and 237 children from Piñon, AZ (Corcoran & Rabin, 1961), investigating similarities to other American Indian tribes and Asian "races" that supported their hypothesis that "American Indian[s] [were] of Mongolian origin" (Nigg, 1925). The results found the O blood type at "unusually high" frequencies in Navajo people, about twice as high as other ethnic populations. The study excluded the "doubtful full bloods" to maintain purity for their analysis (Nigg, 1925). Boyd et al. collected blood from 410 Navajo people living near Ramah, NM to examine the relationship of Rh factor to Asian blood type frequencies and concluded that Navajo individuals mostly have Rh negative factors (Boyd, 1951; Boyd & Boyd, 1949).

Similar to blood types, scientists used HLA-typing to examine population and migration patterns and how certain diseases manifest in humans. HLA genes provide instructions to make surface proteins on cells that react to foreign substances in the blood to fight viral and bacterial infections in the human body. In our search, five studies described HLA typing in relation to

migration and described the similarity of Navajo people to other North American Indigenous groups. The HLA-A, B, C, and DR antigens were analyzed by Troup et al. where they found specific HLA types (n=139 Navajo samples) associated with cancer and diabetes (Troup et al., 1982). Using HLA-B antigen typing, the results showed no variability between North American Indigenous groups but high variability among South American Indigenous groups (Garber et al., 1996; Troup et al., 1982). Three more studies assessed HLA typing in 100 Navajo and Hopi individuals. The first study concluded that Navajo and Hopi people were similar genetically but culturally diverse (Williams et al., 1981). The second found that Reiter's syndrome (found in 13 of 18 Navajo individuals), or reactive arthritis, was associated with HLA-B27 frequency (Morse *et al.*, 1980). Thirdly, sacroiliitis disease (inflammation in one or both of the sacroiliac joints causing pain in the legs) was found to be associated with HLA-B27 as well (Kuberski et al., 1981).

Proteins and enzymes found in the blood were also analyzed in three studies. An analysis of 263 Navajo blood samples showed a high frequency of a new transferrin variant (iron-binding globulins in serum) and comment on how unique the variant frequencies are among the Navajo people compared to other ethnic populations (Parker, 1961). A distinct blood disorder, methemoglobinemia, relates to an overproduction of methemoglobin in erythrocytes, was described in three related Navajo individuals (Balsamo, Hardy, & Scott, 1964). Another study identified a null (silent) allele in glutamate pyruvate transaminase (GPT) in three members of a Navajo family (Crist et al., 1985). In summary, blood/HLA typing, proteins and enzymes in Navajo people were used to make inferences about population similarity, disease associations, and how distinct they were from other Indigenous populations.

Complex Diseases

Seven studies were related to complex or multifactorial diseases that are influenced by the environment and lifestyles. Three studies discussed microvillus inclusion disease, which causes severe diarrhea in infants (Pohl et al., 1999), and has been associated with the gene encoding MYO5B (myosin Vb) (Erickson et al., 2008). All three studies collected blood from 22 Navajo individuals to examine the genetic variants associated with microvillus inclusion disease (Erickson et al., 2008; Knowles et al., 2014; Schlegel et al., 2018). The researchers' findings provide examples that microvillus inclusion disease affects Navajo people at an early age, but the incidence rate remained unknown (Erickson et al., 2008; Pohl et al., 1999).

Three studies reported on several complex diseases: Paget ("bone") disease (n=2), epilepsy (n=2), and the risk of alcoholic liver disease (n=15) (Appavu et al., 2016; Raucy et al., 1999; Whyte et al., 2002). These studies found unique genetic variations in Navajo patients, in particular a homozygous deletion in the *TNFRSF11B* gene associated with bone abnormalities (Morrison, 2018; Whyte et al., 2002) and a unique genetic variant c.121C>T in the *TBC1D24* gene associated with developmental delays and seizures (Appavu et al., 2016). Contrarily, polymorphisms related to CYP2E1 activity and alcoholic liver disease were uninformative and not linked to a predisposition of an alcoholic liver (Raucy et al., 1999).

Lastly, Feeney et al. estimated that Navajo, Apache, and Eskimo children have a greater (5-10 fold) incidence of contracting *Haemophilus influenzae* type b (Hib) compared to the Caucasian population (Feeney et al., 1996). The gene most likely associated with anti-Hib response is *Vk II* gene, and in particular, the *A2* variant in the gene can trigger a detrimental anti-Hib response resulting in a unique *A2b* variant in the *Vk II* gene that showed in 15/28 Navajo individuals (43% heterozygous and 11% homozygous for the A2b variant) and suggested that the

variant may lead to infection with the Hib disease (Feeney et al., 1996). In summary, a total of 69 Navajo people were included in the complex disease studies spanning from 1994-2018.

Forensics

We identified four studies involving forensic genetics. Forensics is the application of science that examines biological evidence from a crime scene to assist the criminal justice system and the law. In the 1990s, the Federal Bureau of Investigation's Combined Index System (CODIS) sponsored a project to create and validate DNA profiles (Budowle & Moretti, 1998; Federal Bureau of Investigation, 2019). Over 21 laboratories across the US and Canada contributed samples to one study of 50 populations, including 187 Navajo people (Budowle & Moretti, 1998). This database was made publicly available and used by Gallo et al. to look at the effects of population structure on probability calculations (the likelihood of identifying a person based upon their DNA profile) in forensic analyses (Gallo et al., 1997) and to verify that the databases were sufficient to identify Native American (including Navajo) individuals using the DNA profiles (Scholl et al., 1996). The probability calculations (or chance of a random match) suggested that researchers were able to identify Navajo individuals based on their DNA profile.

While these studies were used to validate the CODIS system, the data are also accessible to the public. Rohfls et al. used this database to study familial identification across populations, including Navajo individuals (2012). This study concluded that when a sample is searched against a database without an appropriate reference database (inclusive of diverse populations), then relatives and unrelated individuals become more difficult to distinguish when searching the database for a profile match. The study concludes that Navajo individuals look more similar to each other at some of the CODIS loci than other populations, and this had the potential to falsely

lead police to investigate more Navajo family members compared to other populations (Rohlfs, Fullerton, & Weir, 2012).

Hereditary Diseases

Human hereditary diseases can be linked to single or multiple genetic variants that are inherited from parents or arise spontaneously. A total of 25 studies related to hereditary disease were included in our results. Twelve studies were related to the immune system which includes severe combined immunodeficiency disease (SCID)) (Jones et al., 1991; Kwan et al., 2014; Kwan et al., 2015; Li et al., 1998; Li et al., 2002a; Li et al., 2002b; O'Marcaigh et al., 1997) and mtDNA depletion syndrome (also known as neurohepatopathy or neuropathy) (Ortiz et al., 2002; Spinazzola et al., 2008; Vu et al., 2001, El-Hattab et al., 2010, Karadimas et al., 2006). Four studies investigated nonpolyposis colorectal cancer, also known as Lynch syndrome (Lynch et al., 1994; Lynch et al., 1992; Lynch et al., 1996; Lynch et al., 1985). Three studies were related to skin disorders such as poikiloderma (Chantorn & Shwayder, 2012; Clericuzio et al., 2011; Wang et al., 2003). Further, four studies related to the eye were included in our results; diseases such as retinitis, retinoblastoma, and oculocutaneous albinism were described (Berkow & Fleshman, 1983; Heckenlively et al., 1981; Woolf, 1965; Yi et al., 2003). Lastly, one study characterized metachromatic leukodystrophy disease (Pastor-Soler et al., 1994) and another described cystic fibrosis in one Navajo patient (Grebe et al., 1992).

We highlight seven studies about SCIDs that involved Navajo patients spanning 1991-2015 (Jones et al., 1991; Kwan et al., 2014; Kwan et al., 2015; Li et al., 1998; Li et al., 2002a; Li et al., 2002b; O'Marcaigh et al., 1997). SCID is a rare genetic disease that affects the development of T cells which are necessary for combating infections. Newborns are especially

vulnerable and are highly susceptible to severe infections that can lead to death (Kwan et al., 2014). A clinical chart review from 1969-1982 revealed an estimated gene frequency of 2.1% from detailed family genealogies and it was estimated that the highest rate of death due to SCIDs occurred in 1976, affecting an estimated 10% of all infants under 24 months of age (Jones et al., 1991). SCID cases were first phenotypically characterized in 1980 when four cases were reported in "Athabaskan Indians" (Murphy et al., 1980). For the first time, a genetic variant was located in the *IL2RG* gene encoding interleukin-2 receptor γ chain linked to a X-linked maternal inheritance pattern of SCIDs absent of T and B cells in two Navajo patients (O'Marcaigh et al., 1997). An additional 15 cases from "Athabaskan" speaking parents (1 in 2000 live births) were determined to have "SCID-A" (A for Athabaskan) localized to chromosome 10p (Li et al., 1998). A nonsense variant was found in the Artemis protein encoded by *DCLRE1C* gene in six at-risk Navajo people (Li et al., 2002b). Later that year, the same research group published on another type of SCID in the Navajo people (n=18) that exhibited an absence of T and B cells, but normal natural killer cells (Li et al., 2002a). The *Artemis* gene was studied to show it was a nuclear protein and many genetic variants in the exons of the gene were associated with the SCID disease (Li et al., 2002a). This same research team developed and tested the effectiveness of a newborn screening test to detect SCID by analyzing gene byproducts in newborns across the Navajo reservation (Kwan et al., 2014; Kwan et al., 2015) and has since become a part of routine newborn screening for early diagnosis in infants across the US. While many of these SCID studies and newborn screening tests occurred after the moratorium was established, the investigators delicately worked to ensure they were not in violation.

Five hereditary disease studies focused on mitochondrial DNA depletion syndrome (MDS) from 2001-2010 (Ortiz et al., 2002; Spinazzola et al., 2008; Vu et al., 2001; El-Hattab et

al., 2010, Karadimas et al., 2006). Patients with MDS have a deficiency in mitochondria production which can lead to critical organ failure (e.g., in the liver, brain, or kidneys). The first study on MDS examined liver biopsies of two Navajo patients suggesting a defect in a nuclear DNA encoded protein associated with replication of mitochondria (Vu et al., 2001). Shortly after, another Navajo patient with liver damage was diagnosed with MDS and researchers proposed that the MDR3 protein (encoded by *MDR3* gene) may be associated with a non-transcriptional variant (Ortiz et al., 2002). In a study of eight previously studied Navajo samples, Karadimas et al. found the genetic variant R50Q (c.149G>A) in the gene *MVP17* associated with the MDS phenotype (Karadimas et al., 2006; Singleton et al., 1990). Interestingly the MDS disease was labeled as "Navajo neurohepatopathy," implying that this disease is only specific to Navajo people (Karadimas et al., 2006; Ortiz et al., 2002; Vu et al., 2001). However, MDS was later found in Italian populations (Spinazzola et al., 2008). Spinazzola et al. analyzed the *MPV17* and *CAD* genes in Navajo and Italian patients and concluded that the mutation c.149G>A does not appear to have shared origins between the Italian and Navajo populations (2008). A final study detected the same c.149G>A variant in seven Navajo patients and compared their results to other ethnic groups where they found many genetic variants clustered in the region of protein kinase C phosphorylation location on the MPV17 protein, providing further evidence that the MPV17 protein is associated with MDS (El-Hattab et al., 2010).

Four studies examined Lynch syndrome (hereditary non-polyposis colorectal cancer or HNPCC) in Navajo people from 1985-1996 (Lynch et al., 1994; Lynch et al., 1992; Lynch et al., 1996; Lynch et al., 1985). In the 1980s, physicians on the Navajo Nation began to notice a pattern of multiple colorectal cancers in a single family. A pedigree of over 100 extended family members displayed an autosomal dominant inheritance pattern with a high frequency of HNPCC

in affected individuals, despite colorectal cancers being rare in the Navajo population (Lynch et al., 1985). In the late 1990s, the family was revisited and three additional family members presented with HNPCC, leading researchers to investigate the possibility of a genetic link (Lynch et al., 1992). Genetic analysis of two affected family members identified a 4-base pair deletion in the *MLH1* gene, which may be associated with HNPCC (Lynch et al., 1994). Following the detection of the variant in *MLH1*, 51 Navajo patient DNA samples were sequenced, confirming that each affected member had the associated genetic variant (Lynch et al., 1996). Genetic counseling was provided but was challenging for counselors due to the differences in cultural perspectives about genetics and medicine (Lynch et al., 1996).

Three studies published from 2002-2012 investigated poikiloderma (a skin disease manifesting with hyperpigmentation, rashes, nail abnormalities, recurrent infections, and growth deficiency) that affected seven Navajo people, mostly children. These studies suggested a possible association with genetic variants in the *RECQL4* or *C16orf57* genes (Chantorn & Shwayder, 2012; Clericuzio et al., 2011; Wang et al., 2003).

Four studies related to eye disorders have been reported in the Navajo population. One study identified 42 Navajo individuals with the autosomal recessive and 33 with autosomal dominant forms of retinitis pigmentosa (Heckenlively et al., 1981). Retinoblastoma, a malignant cancer of the eye, was reported with a 90% penetrance in affected families with the autosomal dominant form (Berkow & Fleshman, 1983). Albinism, which affects pigmentation and visual acuity was detected in the Navajo population with a prevalence of 1 in 3,750 (Woolf, 1965). This was later confirmed as oculocutaneous albinism type 2 in a study of 142 Navajo individuals to determine the carrier frequency (Yi et al., 2003). The authors stated a different prevalence of 1 in

1,500-2,000, based on allele frequencies of the *OCA2* gene, which harbors a 1.2-kb deletion in the *P* gene (2003).

Finally, a study examined metachromatic leukodystrophy (MLD), an autosomal recessive disorder that phenotypically presents with a deficiency in the lysosomal enzyme arylsulfatase (ARSA) (Pastor-Soler et al., 1994). Six Navajo people with MLD from five different families were found to have a single splice site variant in the *ARSA* gene, but further investigation are needed to find a direct pathophysiological link (Pastor-Soler et al., 1994). Finally, one Navajo patient was diagnosed with a spontaneous form of cystic fibrosis associated with an AA haplotype and has since been the only cystic fibrosis case reported to date (Grebe et al., 1992).

Population Genetics and Migration

One of the fundamental goals of population genetics is to reconstruct the history of modern humans and determine the migration routes and dispersal of global human populations. Researchers study genetic variation within populations to trace gene variant frequency changes over time and space to infer migration patterns. We report 19 studies involving Navajo individuals on mating patterns (four studies from 1953-1998) and population migration (15 studies from 1953-2008).

The studies that relate to mating patterns and inbreeding in the Navajo derive from the extremely detailed genealogical and demographic records collected by anthropologist C. Kluckhohn and colleagues. Data were collected from 1870-1948 from Navajo people residing in Ramah, NM (Spuhler & Kluckhohn, 1953), a non-contiguous Navajo community southeast of the Navajo Nation. The detailed genealogy date back to 1870, when the community was founded by 31 individuals (Hornsby & Mcpherson, 2009) to 1948 when the community consisted of

about 614 individuals. The records spanned 7 generations over 78 years and include 1,105 individuals (Spuhler & Kluckhohn, 1953). These detailed pedigrees allowed researchers to study the relatedness of individuals, including measurements of the degree of inbreeding and made inferences about small, isolated human populations (Allen, 1965; Morgan & Spuhler, 1965; Spuhler, 1989; Spuhler & Kluckhohn, 1953) This data was supplemented with an additional collection of blood samples from 34 Navajo individuals between 1991-1993 for sequencing of 13 dinucleotide repeat loci on chromosomes 9, 10, 11 and 20 (Long et al., 1998). It is not known what type of consents were obtained, if any, although the sensitive nature of the topics should have required community input. These studies concluded that this Navajo community was not highly inbred based upon calculations using a coefficient of inbreeding (the probability of inheriting two copies of the same allele from an ancestor) and Wright's F statistics.

The studies of population migration and population substructure involve specific genetic loci located on the mitochondria (HVI/HVII region), the Y chromosome, and other repeats present in the genome (variable number tandem repeat (VNTR) or ancestry informative biomarkers). Navajo individuals were included in eight studies of mtDNA (Brown et al., 1998; Budowle et al., 2002; Malhi, 2001; Malhi et al., 2002; Malhi et al., 2003; Smith et al., 2000; Torroni et al., 1993; Torroni et al., 1992), three studies of the Y chromosome (Budowle et al., 2005; Malhi et al., 2008; Zegura et al., 2004), and four studies of other loci such as VNTRs, human immunoglobulin GM allotypes, cholinesterase, and D1S80 loci (Balazs, 1993; Duncan et al., 1996; Garry, 1977; Williams et al., 1985). Some of these studies collected samples from Navajo individuals (Brown et al., 1998; Budowle et al., 2005; Budowle et al., 2002; Duncan et al., 1996; Garry, 1977; Smith et al., 2000; Torroni et al., 1992; Zegura et al., 2004) and others relied on publicly available secondary data or samples (Budowle et al., 2002; Malhi, 2001; Malhi

et al., 2002; Malhi et al., 2008; Malhi et al., 2003; Torroni et al., 1993). Some studies may have used modern methods to analyze "orphaned" samples, blood or serum samples collected in the early 1960s and stored for decades in freezers. These studies made inferences from the data about the migration of Navajo people into the Southwest, and how they related to other tribes and populations. Four studies recognize tribal groups in the acknowledgement section with statements such as, "we are indebted to numerous personnel of Indian Health Service Facilities, where most of the samples studied were obtained, as well as to individuals who provided samples used in this analysis and to the Native Americans who authorized their use" (Malhi et al., 2002).

Discussion

Genetic research involving Navajo people has been published over the past 93 years. As genomic technology and methods rapidly advance, there is a need for more robust ethical research practices that address tangible benefits. Important aspects of conducting ethical genetic research include acknowledging Indigenous traditional views about DNA as well as learning about the culture, history, and language. Allowing for other world views and engaging the community can help to promote unbiased research. With this in mind, we discuss the papers in our review and incorporate Navajo traditional knowledge informed by cultural experts and our own cultural teachings.

Diné Heredity and Genetic Knowledge

Navajo people possess a fundamental sense of place which is rooted in *hajíínéí* (their origin story) that establishes a strong relationship with *Diné Bikéyah* (lands of Navajo people) and their

hooghan (traditional homes) within the four sacred mountains that protects the people. In the Navajo worldview, humans are not separate from the land, animals, water, and air that make up our world. We coexist in a state of *hózhǫ́* (beauty and harmony) to maintain balance emotionally, physically, mentally, and spiritually. Individuals who are not in balance increase their risk of acquiring diseases or sickness. Therefore, it is important to consider holistically the entire body and environment to understand Navajo relationality and its role in health (Kahn-John, 2010; Kahn-John & Koithan, 2015).

Navajo people monitor familial relationships through *k'é* a complex genealogical system which takes into account one's clanship, family roles, relationships with different families, and geographic region. A Navajo person has four clans that are inherited from their mother, father's mother, paternal grandfather's mother, and maternal grandfather's mother, respectively. The Navajo clan system guides who one can have relations with (e.g., marriage, partnership, sexual relations) and is, in essence, Navajo peoples' form of genetic inheritance knowledge. This knowledge has been passed down for generations, yet many of the genetic studies involving mtDNA and Y-chromosome patterns of inheritance did not address the clan system.

The environment, diet, and lifestyles that Navajo people live in has changed dramatically with over 200 years of colonization and modernization. First, typical lifestyles have shifted from a nomadic herding and gathering way of life to sedentary lifestyles and westernized diets in just a few generations. Second, *Hwéeldi* (also known as the "Long Walk") was a forced relocation march of Navajo people over 300 miles to Bosque Redondo, NM with subsequent detainment from 1864-1868 (Johnson, 1973). Although written and oral history accounts suggest that many Navajo people fled capture, the population was reduced to 8,000 to 10,000 people, resulting in a population "bottleneck" (Erickson, 1999, 2009; Yi et al., 2003). When Navajo people were

allowed to return to their homelands, the population size eventually expanded to over 350,000 enrolled members today, and certain genetic variants may have increased in frequency leading to a founder effect or genetic drift, a natural process (Kunitz, 1983), in certain communities and an increase in rare conditions and diseases compared to the general population (Li et al., 1998; Lynch et al., 1992; Yi et al., 2003). Third, the US government employed hundreds of Navajo miners to extract uranium from mines constructed on the Navajo Nation to develop nuclear weapons. Many mines remain exposed, which has led to widespread contamination and disease (Brugge et al., 2007; Pasternak, 2010). Finally, infectious diseases have significantly impacted Navajo people, leading to widespread death or altered population demographics. Navajo knowledge and oral histories should be considered in understanding historical interpretations of genetic research studies.

Impact of Genetic Research on Navajo People

Some studies have positively impacted the health of Navajo people. One impactful program emerging from the SCID studies was the implementation of a successful newborn screening program (Erickson, 1999; Jones et al., 1991; Kwan et al., 2014; Kwan et al., 2015; Li et al., 2002b; O'Marcaigh et al., 1997) that has since been adopted by most states across the US. Another positive program is the development of vaccines based on viral and bacterial studies (e.g., *Haemophilus influenzae, Streptococcus pneumoniae*) that are now being used worldwide (Lipsitch et al., 2007; Millar et al., 2005). Of note, some of these studies included Navajo people as co-authors.

Conversely, some population and migration genetic studies raised concerns about the descriptions used in publications. Some studies described Navajo individuals or families as

"doubtful full-bloods" (Nigg, 1925) or "pure stock," in reference to admixture (Lynch et al., 1985), and others describe the ancestors of Navajo people as having a "comparatively meager material and social culture" compared to Puebloan peoples (Malhi et al., 2008). Had input from the Navajo community been sought, these types of biased language could have been avoided. Studies that measured degrees of inbreeding (Allen, 1965; Long et al., 1998; Morgan & Spuhler, 1965; Spuhler, 1989; Spuhler & Kluckhohn, 1953) also raise concerns about exacerbating stereotypes that are viewed as untrue, especially since the Navajo clan system forbids intermarriages. Further, with a legacy of exclusion and displacement from their original lands by white settlers, concerns about using genetics to determine ancestral origins (Eveleth, 2015) can potentially challenge tribe's claims to their lands. Finally, the names associated with some of these diseases are stigmatizing, such as "Navajo Neuropathy" or "Severe Combined Immunodeficiency, Athabascan type." Since the publication of these studies, both diseases have been found in other populations including non-Indigenous, therefore researchers should be cognizant to not label these diseases as Navajo-specific or with community identifiers.

A striking assumption that some blood and HLA typing studies made was that DNA from Navajo people represented other North America Indigenous groups. However, tribes in the US have distinct languages, cultures, histories, and genetic makeups (National Congress of American Indians, 2020). In addition, the publication of the detailed pedigrees of Navajo families from Ramah, NM and in the Lynch syndrome studies could affect the privacy of individuals living in these small communities. Studies about alcoholism and migration should be approached delicately, as there are numerous social, ethical and political implications for tribal communities. For example, studying alcoholism in tribal communities has the potential to perpetuate stereotypes and negatively impact the health and well-being of Navajo people.

Further, many population genetic and migration studies have only assessed a specific region of the genome and at a certain time point to infer their results; we know that the group movement and interactions were dynamic in the past and still continue today.

There are also significant ethical issues both with small sample sizes and continuing to use data that may not have been ethically collected and without the permission of the community and individual. The sample sizes for any given study ranged from one individual to hundreds of Navajo individuals, which raises questions about whether the studies were statistically meaningful for clinical treatment or if they were underpowered and not statistically significant. Such underpowered studies may offer little to no benefit, thus exacerbating concerns about potential secondary uses of samples and data. The practice of sharing samples and data among collaborators, also referred to as "freezer diving," may continue and presents ethical concerns (Kowal, 2013; Merriwether, 1999).

Reach of the Moratorium on Genetic Research

Our results show a general increasing trend in genetic studies in the late 1980's, peaking in 2002, and then decreasing from 2000-2005 (Figure 2). After 2005, the number of studies declines dramatically and are mostly composed of genetic studies relating to bacteria or virus genetics, SCID, and hereditary disease research. This suggests that the moratorium deterred researchers from conducting genetic studies.

Studies that are conducted outside of the Navajo Nation raise questions about the jurisdictional reach of the Navajo Nation. The Navajo Nation Human Research Code states that "research information and data generated by and about Navajo individuals, communities, culture represent inalienable intellectual properties of Navajo people and over which the Navajo Nation

will provide oversight" (Navajo Nation Code, 1994). However, publicly available data and samples may effectively sidestep the Navajo Nation's oversight. For example, the use of CODIS to identify criminal suspects raises concerns about privacy, security, and the biases made when employing these methods across historically underrepresented minority populations. In addition, Navajo patients with rare diseases requiring specialized treatment are often referred off the reservation for treatment where they may be enrolled in genetic research studies. Today, nearly 36% of tribal members live off the Navajo Nation in border towns or metropolitan areas (Navajo Epidemiology Center, 2013), which also complicates the role of tribal research oversight. These are very real concerns that tribes are facing in light of large-scale cohort studies.

With rapidly changing technology and potential genomic research harms, it was the sovereign decision of the Navajo Nation to establish the moratorium to protect their tribal citizens and emergent data. The decision to establish the moratorium was heavily influenced by Navajo traditional healers who uphold that the Navajo human being is sacred, including DNA; therefore, DNA should not be utilized in a harmful way or manipulated with no beneficial outcome. Humans are sacred beings created by *Diyín Diné'e* (the Holy Ones), and it is important for researchers to acknowledge this Navajo worldview. With improved policies and attention to bioethics, an increase in the application of community-based participatory research approaches, and emerging Navajo scientists, there could be an opportunity for Navajo people to benefit from genetic research.

Limitations

We acknowledge that there are limitations to our review. We could only assess studies with a full-text copy available. We evaluated only those studies that specifically included Navajo

individuals according to our search terms; other studies may have used broader definitions such as “American Indians” or “Native Americans” and would have been excluded based upon our criteria. Our summary of the total number of Navajo individuals involved in the research studies is a conservative estimate as some publications were unclear. Table 1 includes the number of individuals or samples that were collected in the first publication of these data and excludes secondarily collected data in the count. Many older studies may also have excluded mentioning approval of IRB, consistent with manuscript publication guidelines or scientific reporting trends of that time. In fact, ethical standards have evolved and changed significantly, and the norms of the past would not be acceptable for researchers today.

Conclusions

In interpreting research results involving Indigenous people, multiple worldviews should be considered to avoid bias and limited viewpoints. We encourage researchers to take into consideration cultural perspectives and traditional knowledge that will not only result in better informed science but also more ethical and respectful science. We hope that more studies will acknowledge and respect Indigenous knowledge by involving more Navajo researchers to co-lead investigations or be included in other aspects of the research process. Many Indigenous researchers are currently being trained in genetic and genomic research methods, many of whom are Navajo (Wade, 2018; Yates, 2019). With stronger collaborations, it will be possible to bridge the gap between Indigenous and Western science.

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Table 1. Summary of 79 Genetic Studies Classified into Bacteria or Virus Genetics, Blood and HLA, Complex Disease, Forensics, Hereditary Disease, Population Genetics and Migration

The table shows the classification of genetic studies that were further separated into various types of disorders, counting the total number of genetic studies that involved the number of Navajo individuals. Note that studies in the blood and HLA category and bacteria or virus category did not sequence human DNA.

Classification	Number of studies	Number of Navajo individuals
Bacteria or virus genetics	**6**	**15,142[a]**
	6	**70[b]**
Blood and Human leukocyte antigen (HLA)	**12**	**1,761**
- blood typing	4	1,104
- HLA typing	5	388
- blood protein/enzyme testing	3	269
Complex diseases	**7**	**69**
- alcoholism	1	15
- epilepsy	1	2
- bone-related disorder	1	2
- microvillus inclusion disease	3	22
- influenza	1	28
Forensics studies	**4**	**263**

Hereditary diseases	**25**	**8,540**
- immune system	12	8,039
- cancer	4	230
- eye-related disorders	4	248
- skin-related disorders	3	7
- metabolic disorder	1	15
- cystic fibrosis	1	1
Population genetics and migration	**19**	**2,652**
- inbreeding or mating patterns	4	1,202
- migration/population Substructure	15	1,450
TOTAL	**79**	**13,355**

[a]Six related studies used samples collected from Navajo people and White Mountain Apache children spanning from 1994-2009. Some studies did not report the number of Navajo individuals and simply reported aggregate data from multiple tribes, meaning the number does not distinguish between different tribal groups. We report the highest total number reported as it was unclear which samples were shared or unique to the studies.

[b]Six studies included a total of 70 Navajo samples.

Supplementary Table S1. Summary Characteristics of All Genetic Studies Involving Navajo Individuals

Table summarizes all studies in alphabetical order according to the first author's last name. Then, we report the year of publication, publisher, study classification, name of disease or topic, gene or chromosome sequenced, tribal and institutional approval status, total number of Navajo individuals included in each study, whether the study occurred on or off of the Navajo Nation, and if the data were original or secondary (not directly collected by researchers).

First Author (Last Name, First Initial, Middle Initial)	Year	Publisher	Classification	Name of disease or general topic	Gene(s) or chromosome region	Type of tribal approval (NNHRRB, tribal, Native Health board)	Academic Institutional Approval (Yes/NM)	Number of Navajo individuals included	Study location (On, Off, or NM)
Agostini, H.T.	1997	*Proceedings of the National Academy of Science*	Bacteria/Virus	Human polyomavirus JC (JCV)	polyomavirus	NM	NM	64	NM
Allen	1965	*Eugenics Quarterly*	Population Genetics	inbreeding	NA	NM	NM	1,118[b]	On
Appavu, B.	2016	*Epileptic Disorders*	Complex Disease/epilepsy	Epilepsy	*TBC1D24*	NM	Yes	2	Off
Azarian, T.	2018	*PLOS pathogens*	Bacteria/Virus	Streptococcus pneumoniae	bacteria	NNHRRB, Phoenix Area Indian Health Service, White Mountain Apache tribe approved	Yes	937[a]	On
Balazs, I.	1993	*EXS*	Population Genetics	Migration/Population Substructure	VNTR loci	NM	NM	83[b]	Off
Balsamo, P.	1964	*Journal of Pediatrics*	Blood and HLA Types	methemoglobinemia	NA	NM	NM	3	On
Berkow, R.L.	1983	*American Journal of Diseases of Children*	Hereditary/eye	Retinoblastoma	NA	NM	NM	6	On and Off
Biggar, R.J.	1995	*Virology*	Bacteria/Virus	Human T-cell lymphotropic virus Type II	retroviruses	NM	NM	1[b]	Off
Boyd, W.	1949	*American Journal of*	Blood and HLA Types	blood types, Rh gene, and phenyl-thio-carbamide (PTC)	NA	NM	NM	361	On

		Physical Anthropology							
Boyd, W.	1951	*Science American*	Blood and HLA Types	Rh gene	NA	NM	NM	410[b]	NM
Brown, M.D.	1998	*American Journal of Human Genetics*	Population Genetics	Migration/Population Substructure	mtDNA	NM	NM	4 (this study), 2[b]	Off
Budowle, B.	1998	*9th International Symposium on Human Identification*	Forensic	Forensics	STR typing (CODIS markers)	NM	NM	182	Off
Budowle, B.	2002	*International Journal of Legal Medicine*	Population Genetics	Migration/Population Substructure	mtDNA	NM	NM	146	Off
Budowle, B.	2005	*Forensic Science International*	Population Genetics	Migration/Population Substructure	Y-chromosome	NM	NM	219	NM
Chantorn, R.	2012	*Pediatric Dermatology*	Hereditary/skin	Poikiloderma with Neutropenia	*C16orf57*	NM	NM	1	NM
Clericuzio, C.	2011	*American Journal of Medical Genetics*	Hereditary/skin	Poikiloderma with Neutropenia	*C16orf57*	NM	Yes	4	NM
Corcoran, P.A.	1961	NA	Blood and HLA Types	blood group	NA	NM	NM	237	On
Crist, M.	1985	*Human Heredity*	Blood and HLA Types	decrease in an enzyme	*GPT* null allele	NM	NM	3	Off
Duncan, G.	1996	*Genetica*	Population Genetics	Migration/Population Substructure	*D1S80*	NM	NM	28 (this study) and 72[b]	On
El-Hattab, A.W.	2010	*Molecular Genetics and Metabolism*	Hereditary/immune disease	mtDNA depletion syndrome	*MPV17*	NM	NM	1	NM
Erickson, R.P.	2008	*American Journal of Medical Genetics*	Complex Disease/MVID	Microvillous inclusion disease	*MYO5B*	NM	Yes	13	NM
Feeney, A.J.	1996	*Journal of Clinical Investigation*	Complex Disease/ influenzae	Haemophilus influenzae type b	*A2 Vkappa* gene	NM	NM	28	Off for controls; NM for

									affected samples
Fernandez-Cobo, M.	2002	*American Journal of Physical Anthropology*	Bacteria/Virus	Human polyomavirus JC (JCV)	polyomavirus	NM	NM	68[b]	NM
Gallo, J.C.	1997	*Genetica*	Forensic	Forensics	*HLA-DQA1*, *LDLR*, *GYPA*, *HBGG*, *D7S8*, *Gc*, and *D1S80*	NM	NM	81[b]	On and Off
Garber, T.L.	1996	*Tissue Antigens*	Blood and HLA Types	HLA typing	*HLA-B*	NM	NM	41	On
Garry, P.J.	1977	*Human Heredity*	Population Genetics	Migration/Population Substructure	fluoride-resistant genes	NM	NM	358	On
Grant, L.	2012	*Pediatric Infectious Disease*	Bacteria/Virus	rotavirus	bacteria	NNHRRB and Phoenix Area Indian Health Service approved	Yes	584	On
Grant, L.	2011	*Pediatric Infectious Disease*	Bacteria/Virus	Rotavirus vaccine	rotavirus	NNHRRB, Phoenix Area Indian Health Service, White Mountain Apache tribe approved	Yes	NM	On
Grebe, T.A.	1992	*American Journal of Human Genetics*	Hereditary/cystic fibrosis	Cystic Fibrosis	*CFTR*	NM	NM	1	Off
Heckenlively, J.	1981	*Metabolic and Pediatric Ophthalmology*	Hereditary/eye	Retinitis Pigmentosa	NA	NM	Yes	76	On
Hjelle, B.	1993	*Journal of Infectious Diseases*	Bacteria/Virus	Human T-cell lymphotropic virus Type II	retroviruses	NM	NM	4	Off
Jones, J.F.	1991	*Human Biology*	Hereditary/immune disease	SCID	NA	NM	NM	18	On
Karadimas, C.L.	2006	*American Journal of Human Genetics*	Hereditary/ immune disease	Navajo Neurohepatopathy	*MPV17*	NM	Yes	8	NM
Knowles, B.C.	2014	*Journal of Clinical Investigation*	Complex Disease/MVID	Microvillus Inclusion disease	*MYO5B*	NM	Yes	5	Off

Kuberski, T.T.	1981	*Human Immunology*	Blood and HLA Types	HLA and sacroiliitis	*HLA-B27, HLA-Cw1, HLA-Cw2*	NM; Thanked Navajo and Hopi tribes	NM	108 (this study), 100[b]	On
Kwan, A.	2014	*Journal of American Medical Association*	Hereditary/ immune disease	SCID	*DCLRE1C*	NM	Yes	3,498	On
Kwan, A.	2015	*Clinical Immunology*	Hereditary/ immune disease	SCID	*DCLRE1C*	NNHRRB approved	Yes	4,405	On
Li, L.	2002	*Prenatal Diagnostics*	Hereditary/ immune disease	SCIDA	*Artemis*	Navajo Nation Health Board approved	Yes	36	On and Off
Li, L.	1998	*American Journal of Human Genetics*	Hereditary/ immune disease	T-B- SCID	chromosome 10p	Navajo Nation Health Board approved	Yes	15	On and Off
Li, L.	2002	*Immunology*	Hereditary/ immune disease	T-B-NK+ SCID	*SNM1*-like gene, *Artemis*	Navajo Nation Health Board approved	Yes	48	On and Off
Lipsitch, M.	2007	*The Journal of Infectious Diseases*	Bacteria/Virus	Streptococcus pneumoniae	bacteria	NNHRRB, Phoenix Area Indian Health Service, and National Indian Health Service approved	Yes	590[a]	On
Long, J.	1998	*Journal of Mammalogy*	Population Genetics	Inbreeding	pedigrees	NM	NM	84 (this study), 1,118[b]	On and Off
Lynch, H.T.	1985	*Cancer Genetics and Cytogenetics*	Hereditary/cancer	hereditary nonpolyposis colorectal cancer (HNPCC)	NA	NM	Yes	62	On
Lynch, H.T.	1992	*American Indian Culture and Research Journal*	Hereditary/cancer	hereditary nonpolyposis colorectal cancer (HNPCC)	NA	NM	NM	17	On
Lynch, H.T.	1994	*Journal of the National Cancer Institute*	Hereditary/cancer	hereditary nonpolyposis colorectal cancer (HNPCC)	*MLH1*	NM	NM	>100	On
Lynch, H.T.	1996	*Cancer*	Hereditary/cancer	hereditary nonpolyposis colorectal cancer (HNPCC)	*MLH1*	NM	Yes	51[b]	On
Malhi, R.S.	2001	*PhD thesis, University of*	Population Genetics	Migration/Population Substructure	mtDNA	NM	NM	64[b]	On and Off

		California, Davis							
Malhi, R.S.	2002	*American Journal Human Genetics*	Population Genetics	Migration/Population Substructure	mtDNA	NM; Thanked Indian Health Services and Native Americans	NM	64[b]	On and Off
Malhi, R.S.	2003	*American Journal of Physical Anthropology*	Population Genetics	Migration/Population Substructure	mtDNA	NM; Thanked Indian Health Services and Native Americans	NM	2[b]	On and Off
Malhi, R.S.	2008	*American Journal of Physical Anthropology*	Population Genetics	Migration/Population Substructure	Y-chromosome	NM; Thanked Indian Health Services and Native Americans	NM	75[b]	On and Off
Millar, E.V.	2005	*Clinical Infectious Diseases*	Bacteria/Virus	Influenza type b	bacteria	NNHRRB and Phoenix Area Indian Health Service approved	Yes	15,142[a]	On
Morgan	1965	*Eugenics Quarterly*	Population Genetics	Inbreeding	pedigrees	NM	NM	1,118[b]	On
Morse, H.	1980	*Journal of Rheumatology*	Blood and HLA Types	HLA and Reiter's Syndrome	*HLA B27*	NM; Thanked Navajo and Hopi tribes	NM	100	On
Nigg, C.	1925	*Journal of Immunology*	Blood and HLA Types	blood types	NA	NM; Thanked Superintendent of Indian Education, Bureau of Indian Affairs, Superintendent of Ft. Defiance School	NM	457	On
O'Marcaigh, A.S.	1997	*Journal of Clinical Immunology*	Hereditary/ immune disease	SCID X-linked	*IL2RG*	NM	NM	2	NM
Ortiz, D.	2002	*American Association for the Study of Liver Disease*	Hereditary/ immune disease	Navajo neuropathy, mRNA deficiency	*MDR3*	NM	NM	1	NM
Parker, W.C.	1961	*Science*	Blood and HLA Types	haptoglobin and transferrin types	NA	NM	NM	263	NM
Pastor-Soler, N.M.	1994	*Human Mutation*	Hereditary/ metabolism	metachromatic leukodystrophy (MLD)	*arylsulfatase A* gene	NM	NM	15	NM

Raucy, J.L.	1999	*Alcoholic clinical and experimental research*	Complex Disease/ alcoholism	alcoholism	*CYP2E1* in P-450	NM	Yes	15	Off
Rohlfs, R.	2012	*PLOS Genetics*	Forensic	Forensics	STR typing (CODIS markers)	NM	NM	182[b]	Off
Schlegel, C.	2018	*Digestive Diseases and Sciences*	Complex Disease/MVID	microvillus inclusion disease	*MYO5B*	NM	Yes	4	Off
Scholl Susan	1996	*Journal of Forensic Sciences*	Forensic	Forensics	*HLA-DQA1*, *LDLR*, *GYPA*, *HBGG*, *D7S8*, *Gc*, and *D1S80*	NM	NM	81	On and Off
Scott, J.R.	2012	*The Journal of Infectious Disease*	Bacteria/Virus	Pneumococcal vaccination	bacteria	NM	NM	208[a]	On
Scott, J.R.	2012	*Vaccine*	Bacteria/Virus	Pneumococcal vaccination	bacteria	NNHRRB, Phoenix Area Indian Health Service, White Mountain Apache tribe approved	Yes	391[a]	On
Smith, D.G.	2000	*American Journal of Physical Anthropology*	Population Genetics	Migration/Population Substructure	mtDNA	NM; Thanked Indian Health Services and Native Americans	NM	292	On and Off
Spinazzola, A.	2008	*Neuromuscular disorders*	Hereditary/ immune disease	mitochondrial DNA depletion syndrome	*MPV17* and *CAD*	NM	NM	5	NM
Spuhler, J.N.	1953	*Human Biology*	Population Genetics	Inbreeding	pedigrees	NM	NM	1,118	On
Switzer, W.M.	1995	*Journal of Virology*	Bacteria/Virus	Human T-cell lymphotropic virus Type II	retroviruses	NM	NM	2	NM
Torroni, A.	1992	*Genetics Society of American*	Population Genetics	Migration/Population Substructure	mtDNA	NM	NM	48	On and Off
Torroni, A.	1993	*American Journal Human Genetics*	Population Genetics	Migration/Population Substructure	mtDNA	NM	NM	48[b]	On and Off
Troup, G.M.	1982	*Tissue Antigens*	Blood and HLA Types	HLA typing	*HLA-A, B, C, DR*	NM	NM	139	Off

Vu, T.H.	2001	*Hepatology*	Hereditary/ immune disease	Navajo Neurohepatopathy	mtDNA	NM	Yes	2	NM
Wang, L.L.	2003	*American Journal of Medical Genetics*	Hereditary/skin	Poikiloderma with neutropenia	*RECQL4*	NM	Yes	2	NM
Whyte, M.P.	2002	*New England Journal of Medicine*	Complex Disease/bone disease	Paget Disease	*TNFRSF11B*	NM	NM	2	NM
Williams, R.C.	1981	*American Journal of Physical Anthropology*	Blood and HLA Types	HLA typing	*HLA-A, B, C, DR*	NM	Yes	100[b]	On
Williams, R.C.	1985	*American Journal of Physical Anthropology*	Population Genetics	Migration/Population Substructure		NM	NM	193	Off
Woolf, C.M.	1965	*American Journal of Human Genetics*	Hereditary/eye	Albinism	NA	NM	Yes	24	On
Yi, Z.	2003	*American Journal of Human Genetics*	Hereditary/eye	Oculocutaneous albinism	*P* and *MATP* genes	NM	Yes	142	On
Zegura, S.L.	2004	*Society of Molecular Biology and Evolution*	Population Genetics	Migration/Population Substructure	Y-chromosome	NM	Yes	78	NM

[a]Six related studies used samples from the same dataset collected from Navajo and White Mountain Apache children spanning from 1994-2009. The number does not distinguish between different tribal groups.

[b]Secondary data used from a previously published dataset or shared samples.

mtDNA: mitochondrial DNA, MVID: microvillus inclusion disease or mtDNA depletion syndrome, NNHRRB: Navajo Nation Human Research Review Board, NA: not available, NM: not mentioned.

Figure Captions

Figure 1. Literature search flowchart. Search methods diagram showing the number of included and excluded genetic research studies along with the number of studies for each of the six classifications with definitions of the study types.

Figure 2. Publication timeline of genetic studies involving Navajo individuals. The timeline spans 1925-2018 in five-year intervals to depict the frequency of genetic studies. The establishment of the Navajo Nation Human Research Review Board in 1996 is depicted by a vertical black line. The moratorium on genetic research on Navajo Nation was established in 2002, depicted by a vertical blue line. Blood and HLA studies (shown in orange) and the bacteria or virus studies (shown in yellow) were separated into different groups since these studies did not use genetic technology or sequence human DNA. All other studies (shown in light blue) sequenced or analyzed human DNA from Navajo individuals.

Figure 1.

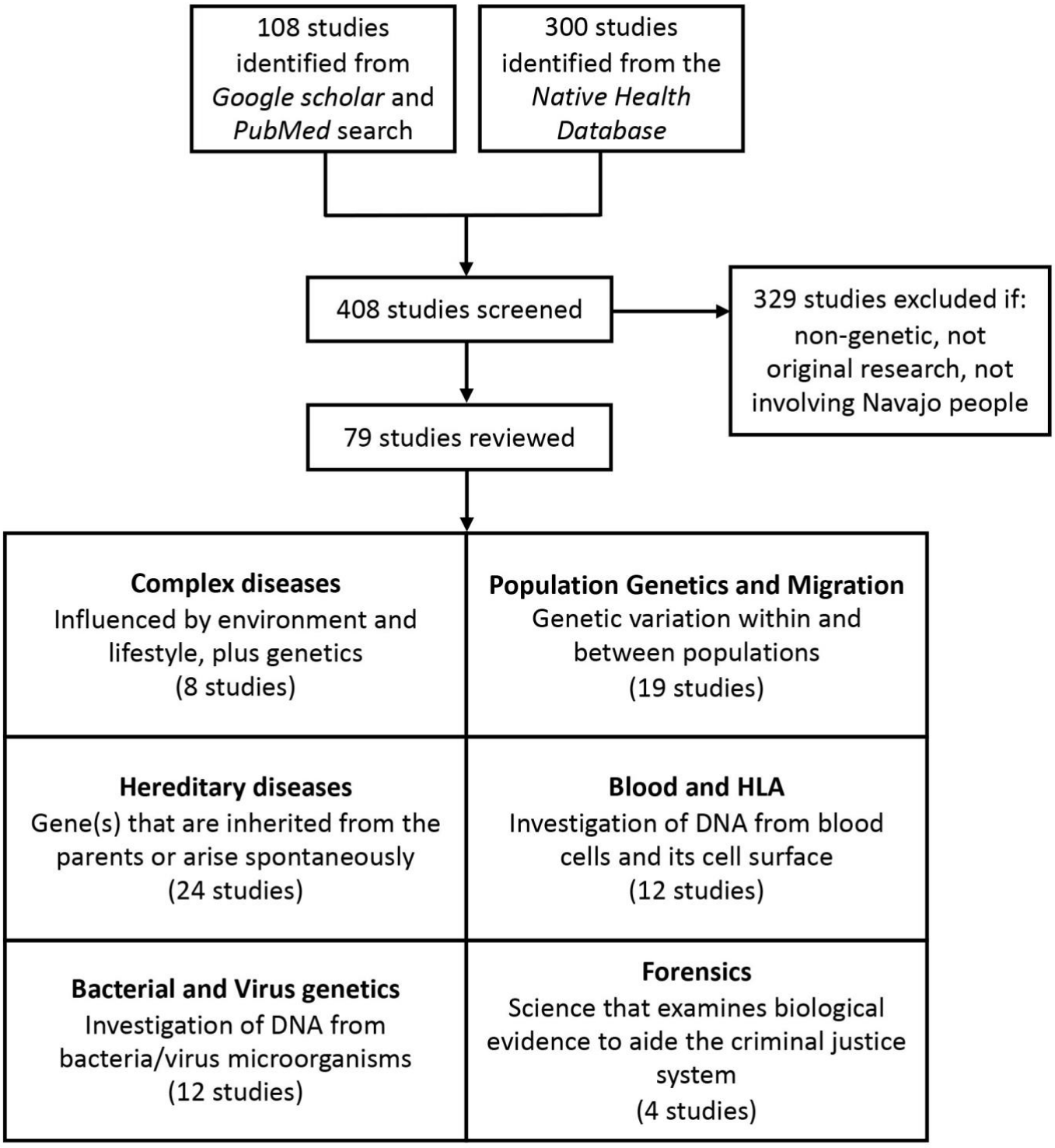

Figure 2.