BRIEF COMMUNICATION | Genetics in Medicine

The limited use of US residual newborn screening dried bloodspots for health disparity research

Naomi O. Riches, PhD[1], Erin P. Johnson, PhD[2], Caren J. Frost, PhD, MPH[3], Aaron J. Goldenberg, PhD[4] and Erin Rothwell, PhD[2]

Purpose: State-run newborn screening programs screen nearly all babies born in the United States at the time of delivery. After newborn screening has been completed, some states store the residual dried bloodspots. It is unknown how they have been used to address health disparities–related research.

Methods: In 2017–2018, a scoping review was conducted to evaluate the extent, type, and nature of how residual dried bloodspots. The review included 654 eligible publications, worldwide, published before May 2017. A post hoc analysis of the US-based studies using residual dried bloodspots ($n = 192$) were analyzed.

Results: There were 32 (16.7%) articles identified that studied a condition of a known health disparity or focused on a key population: 25 studies assessed a disease or condition, 6 expressly enrolled a key population, and 1 study included both (i.e., heart disease and African American/Black).

Conclusion: Excluding 12 studies that researched leukemia or a brain tumor, only 20 studies addressed a known health disparity, with 6 stating a specific aim to address a health disparity. This resource could be used to gain further knowledge about health disparities, but is currently underutilized.

Genetics in Medicine (2020) 22:1723–1726; https://doi.org/10.1038/s41436-020-0858-6

Keywords: newborn screening; health disparities; scoping review; residual dried bloodspots

INTRODUCTION

The US National Institutes of Health (NIH) identified key diseases, chronic illnesses, and health outcomes that unequally burden specific populations, including diabetes, heart disease, cancer, stroke, substance abuse, HIV/AIDS, infant mortality, low birth weight, and shorter life expectancy.[1] There have been multiple calls for increased support for research aimed at identifying and understanding the biological, environmental, and social determinants that lead to these health disparities. However, the populations most impacted by health disparities, including racial and ethnic minority communities and other underserved groups, are vastly underrepresented in biological and health data repositories used for research. In response, efforts to promote precision medicine and translational research have made the inclusion of underrepresented populations a primary goal. While the inclusion of underserved populations in research will not alone "fix" the health inequities they experience, it is an important step toward creating a more representative research infrastructure that is better prepared to study health disparities.

To meet this challenge, large population databases and cohort studies are working to enroll underrepresented groups; however, there is also an increased need to use already existing resources that may be more representative than typical biorepositories. One such resource is one of the oldest and most successful public health systems in the United States: state newborn screening programs.

Newborn screening (NBS) programs have universally tested all newborns for treatable diseases, beginning in the 1960s, with the advent of the phenylketonuria assay. NBS programs identify children who have a metabolic or genetic condition that would benefit from early intervention, which in turn, prevents severe morbidity or mortality.[2] These programs represent one of the only health screens universally available to all families in the United States and, therefore, have been seen by many to help address population-level disparities, especially within the context of rare diseases.[3]

Along with their public health and clinical benefits, NBS programs have also inadvertently created a valuable resource for research. Mandatory NBS programs exist in all 50 states and screen the vast majority of newborns at the time of delivery regardless of their race, socioeconomic status, or geography. The leftover, or residual, dried bloodspots (DBS) create an immense biorepository that could be made available for research. After NBS has been completed, most leftover

[1]Department of Biomedical Informatics, University of Utah, Salt Lake City, UT, USA; [2]Department of Ob/Gyn, School of Medicine, University of Utah, Salt Lake City, UT, USA; [3]College of Social Work, University of Utah, Salt Lake City, UT, USA; [4]Department of Bioethics, School of Medicine, Case Western Reserve University, Cleveland, OH, USA. Correspondence: Erin Rothwell (erin.rothwell@hsc.utah.edu)

Submitted 7 January 2020; accepted: 27 May 2020
Published online: 12 June 2020

DBS are stored for months or years in some states. The sheer number and representativeness of these samples could be utilized as an invaluable source of data to study health disparities. The very nature of these collections is inherently diverse, and can ensure that research include individuals of all backgrounds in their studies.[3] Unfortunately, few states have the resources to store and retain DBS for research and it is unclear how DBS have been used to address health disparities–related research. This review examines how researchers have used NBS DBS to explore diabetes, heart disease, cancer, stroke, substance abuse, HIV/AIDS, infant mortality, and low birth weight, all diseases that have been identified as unequally burdening specific populations.

MATERIALS AND METHODS

In 2017–2018, our research team conducted a scoping review to evaluate the extent, type, and nature of how residual DBS from NBS programs are used in research. The review included 654 eligible publications worldwide, published before May 2017. Materials and methods are described in a previous article.[4]

Eligibility criteria

From the original set of 654 peer-reviewed journal articles, we limited this current review to research on residual DBS from US NBS programs, which resulted in 192 eligible publications.[4] Each of these was reviewed to identify those exploring a (1) condition that unequally burdens specific populations, creating a health disparity (diabetes, heart disease, cancer, stroke, substance abuse, HIV/AIDS, and low birth weight) or (2) key population (African American/Black, Hispanic/Latino, American Indian and Alaska Natives, Asian Americans, Pacific Islanders, and Native Hawaiians).[1,5]

Data management and extraction

The secure, web-based software platform REDCap (Research Electronic Data Capture) was used in the previous scoping review.[6] For this review, we added additional questions about the target health disparities and key populations to the REDCap database (see Table 1). We then applied these ten questions to the 192 publications previously identified as using DBS from US-based NBS programs. Once studies were identified, we distinguished beween studies that addressed health disparities from those that specifically did.

RESULTS

Of the 192 studies included in this systematic review, representing all of the published research using NBS DBS in the United States, 32 (16.7%) of the published articles studied a known health disparity condition or focused on a key population. Twenty-five of those studies explored one of the identified diseases or conditions (i.e., diabetes, cancer, heart disease, HIV/AIDS, low birth weight, stroke, or substance abuse), six expressly enrolled a key population (i.e., African American/Black, Hispanic/Latino, diversity in general), and one study included both (i.e., heart disease and African American/Black).

Table 1 Number and percentage of studies included, by health disparity or key population question.

Data query	Yes (*n*)	% of included studies (32)	% of total (192)
Does this study address the diversity of the sample?	7	21.9%	3.6%
Did they report on sex breakdown?	13	40.6%	6.8%
Did they report on race?	17	53.1%	8.9%
Did they report on ethnicity?	10	31.3%	5.2%
Did they mention the inclusion of underrepresented persons?	7	21.9%	3.6%
Does this study mention how representative their population is compared to the whole community? (Is it a cross-section of the population? or Did they include language about generalizability?)	7	21.9%	3.6%
Was a specific aim to explore a disparity or key population?	6	18.8%	3.1%
Does this study mention if the use of newborn screening bloodspots is a good source to address health or population disparities?	2	6.3%	1.0%
Was zip code data used to find a specific population?	0	0%	0%
Was a chronic disease researched in this study?	5	15.6%	2.6%

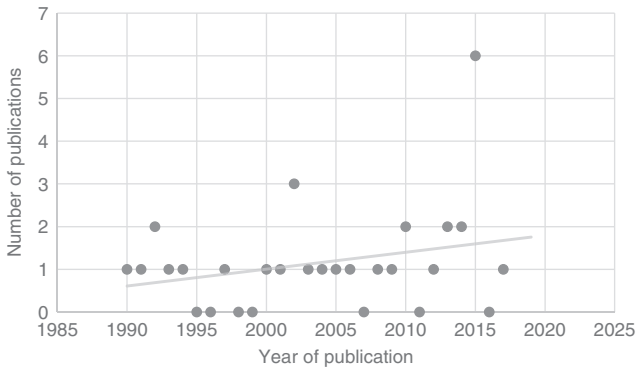

Fig. 1 Number of publications studying a topic considered a health disparity or key population by year.

Figure 1 shows the publication year of each of the 32 studies found to include a health disparity or key population. The number of publications have been fairly consistent, between zero and three, over time with the exception of 2015, which had six publications.

Six of the studies expressly enrolled a key population: African American/Black ($n = 1$), Hispanic/Latino ($n = 2$), and diverse populations in general ($n = 4$). An additional

26 studies explored a condition or disease that is a known health disparity. The conditions/diseases identified were cancer, heart disease, HIV/AIDS, low birth weight, and substance abuse. The majority of those conditions identified were cancers ($n = 13$). However, some types of cancers, which disproportionately affect children, are thought to be distinct from cancers generally diagnosed in adults. Cancers such as leukemias and brain tumors are thought to be of genetic origin, versus those later diagnosed, which are associated more often with lifestyle or environmental exposure.[7] When leukemias ($n = 9$) and brain tumors ($n = 3$) were separated from the cancer variable, only one study remained, which targeted a population with cancer (adult testicular germ cell tumors). Five studies researched a chronic disease. However, only 6 (3.1% of the total 192) of the 32 studies specifically stated an aim to address a health disparity or key population, with 2 of those studies explicitly mentioning DBS as a good source to address a health disparity. Overall, the 32 studies that enrolled a key population or explored a known health disparity condition were more likely to report on sex, race, and ethnicity than the total 192 US studies (sex: 40.6% vs. 6.8% of the total; race: 54.8% vs. 8.9% of the total; and ethnicity: 31.3% vs. 5.2% of the total, respectively).

For the purposes of this Brief Communication, we cite here the six studies that explicitly stated an aim to explore a health disparity or key population. Conroy et al.[8] investigated the prevalence of four genetic variants associated with venous thromboembolism among African American, Hispanic, and Caucasian people born in New York.[8] Drury et al.[9] compared newborn telomere length between races of an ethnically diverse population of the greater New Orleans area.[9] Hughes et al.[10] tested the validity of using an Illumina MiSeqDxCF 139-variant assay on an ethnically diverse set of known cystic fibrosis newborns.[10] Jacobson et al.[11] examined the prevalence of the amyloidogenic transthyretin V122I allele, a gene associated with amyloidosis, in African Americans from New York State.[11] Kharrazi et al.[12] inspected the birth prevalence of congenital cytomegalovirus within the Hispanic community of California.[12] Finally, Sartippour et al.[13] sought to detect the IVS2-2 variant of galactose-1-phosphate uridyl transferase gene among California Hispanics.[13] Of these six studies, five reported on the diversity of the sample and race breakdown. Sex and ethnicity were reported in three of the publications, and one study researched a chronic condition. Five of the six studies assessed the prevalence of a disease or gene, and three selected DBS from a targeted population.

DISCUSSION

This review identified the limited use of NBS DBS to address diseases and populations associated with health disparities in the United States. The 2019 scoping review identified 192 studies using NBS DBS in the United States before May 2017.[4] The diseases most studied in those projects were inborn genetic diseases (52.1%), most of which do not disproportionately affect key populations. While 32 of the 192 studies in this review explored either a disease/condition that unequally burdens specific populations (health disparity) or focused on a key population, 12 of those researched leukemia or brain tumors, which are typically genetically caused. Excluding those studies, the remaining 20 (10.4%) publications had the potential to address health disparities in their analysis of the NBS DBS. However, only six studies (3.1%) stated a specific aim to address a health disparity. Of these six publications, only one addressed a chronic condition, heart disease, where researchers examined the prevalence of the amyloidogenic transthyretin V122I variant among African Americans, which is associated with heart disease, as well as several other health outcomes.[11] While Sartippour et al. specified an aim to find the prevalence of the IVS2-2 variant of galactose-1-phosphate uridyl transferase gene within a key population (Hispanics), this information was only briefly discussed.[13]

NBS DBS are a rich source of racially, ethnically, and socioeconomically diverse samples that have been underutilized by those interested in addressing health disparities in the United States. The National Institute of Child Health and Development's Newborn Screening Translational Research Network is working to make NBS DBS available, with the proper permissions and privacy protections, to researchers.[14] With an ever-changing and diversifying population in the United States, it is more important than ever to find ways to better understand the causes of health disparities to develop and implement cultrually appropriate education and interventions for care. While DBS alone cannot fully elucidate the causes and solutions to all health disparities, especially concerning social determinants of health, these specimens could provide crucial information in assessing genetic and other biological factors as well as measuring environmental exposures that impact population prevalence and burden of many diseases disproportionately affecting underrepresented populations.

While the NBS program provides a rich source of material for important health disparity research, the future of the availability of these samples may be at risk. Lawsuits in Minnesota and Texas provide lessons learned for how DBS can be used for research. Both states have now implemented a consent process for storage and use of NBS DBS. Research indicates that parents want to be asked and when asked are supportive of research using DBS.[15] However, there is now a need for better patient education to ensure participants are making informed choices. There is also an increased need to identify and demonstrate the utility and value of these samples as resources for health research generally, and more specifically disparities research, in national debates over the storage and use of DBS.

Limitations

A limitation of this study is that it is difficult to define the intentions of the authors regarding their inclusion of key populations or disease focus. Additional articles beyond the six we identified may have had an intent to address a health disparity.

Conclusion

Due to the paucity of health disparity research conducted with NBS DBS, there exists an opportunity to expand our public health knowledge using these samples. Nevertheless, these studies highlighted how NBS DBS could be used to gain further knowledge about diseases that disproportionately affect those commonly experiencing health disparities. This underutilized resource could play an important role in identifying and addressing key health or population disparities by providing copious samples from diverse populations.

DISCLOSURE

The authors declare no conflicts of interest.

REFERENCES

1. National Institutes of Health. NIH fact sheet: health disparities. 2018. https://archives.nih.gov/asites/report/09-09-2019/report.nih.gov/nihfactsheets/ViewFactSheet2666.html?csid=124&key=H#H. Accessed 13 August 2019.
2. Waisbren SE, Albers S, Amato S, et al. Effect of expanded newborn screening for biochemical genetic disorders on child outcomes and parental stress. JAMA. 2003;290:2564–2572.
3. Brosco JP, Grosse SD, Ross LF. Universal state newborn screening programs can reduce health disparities. JAMA Pediatr. 2015;169:7–8.
4. Rothwell E, Johnson E, Riches N, Botkin JR. Secondary research uses of residual newborn screening dried bloodspots: a scoping review. Genet Med. 2019;21:1469–1475.
5. National Institute on Minority Health and Health Disparities. Overview. 2015. https://www.nimhd.nih.gov/about/overview/. Accessed 24 February 2020.
6. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42:377–381.
7. Dana Farber Cancer Institute. What is the difference between cancer in adults and cancer in children? 2018. https://blog.dana-farber.org/insight/2018/09/difference-cancer-adults-cancer-children/. Accessed 13 August 2019.
8. Conroy JM, Trivedi G, Sovd T, Caggana M. The allele frequency of mutations in four genes that confer enhanced susceptibility to venous thromboembolism in an unselected group of New York State newborns. Thromb Res. 2000;99:317–324.
9. Drury SS, Esteves K, Hatch V, et al. Setting the trajectory: racial disparities in newborn telomere length. J Pediatr. 2015;166:1181–1186.
10. Hughes EE, Stevens CF, Saavedra-Matiz CA, et al. Clinical sensitivity of cystic fibrosis mutation panels in a diverse population. Hum Mutat. 2016;37:201–208.
11. Jacobson DR, Alexander AA, Tagoe C, Buxbaum JN. Prevalence of the amyloidogenic transthyretin (TTR) V122I allele in 14 333 African-Americans. Amyloid. 2015;22:171–174.
12. Kharrazi M, Hyde T, Young S, et al. Use of screening dried blood spots for estimation of prevalence, risk factors, and birth outcomes of congenital cytomegalovirus infection. J Pediatr. 2010;157:191–197.
13. Sartippour MR, Doroudian R, Frampton G, et al. Identification of galactose-1-phosphate uridyl transferase gene common mutations in dried blood spots. Clin Chim Acta. 2014;436:298–302.
14. Eunice Kennedy Shriver National Institute of Child Health and Human Development. Newborn Screening Translational Research Network (NBSTRN): overview. 2017. https://www.nichd.nih.gov/research/supported/nbstrn. Accessed 23 August 2019.
15. Rothwell E, Johnson E, Wong B, et al. Comparison of video, app and standard consent processes on decision-making for biospecimen research: a randomized controlled trial. J Empir Res Hum Res Ethics. 2020 Apr 3; https://doi.org/10.1177/15562620913455 [Epub ahead of print].