The University of Wisconsin Undiagnosed Disease Program: Unveiling Rare Neurodevelopmental Disorders in Exome-Negative Patients

Jadin M. Heilmann; April L. Hall, PhD, MS, CGC; Janet M. Legare, MD; Gregory M. Rice, MD; Kristin A. Seaborg, MD; Derek M. Pavelec, PhD; Xiangqiang Shao, PhD; Vanessa Horner, PhD; M. Stephen Meyn, MD, PhD; Bryn D. Webb, MD

ABSTRACT

Introduction: The University of Wisconsin Undiagnosed Disease Program employs a "beyond the exome" approach to diagnose rare disease patients.

Case Presentations: We present 2 cases of rare neurodevelopmental disorders identified by whole genome sequencing. The first is a 12-year-old boy with global developmental delay/intellectual disability (GDD/ID) and congenital hypotonia who was diagnosed with *CAPZA2*-related disorder. The second is a 13-year-old boy with microcephaly, GDD/ID, and seizures who was diagnosed with neurodevelopmental disorder with language delay and behavioral abnormalities, with or without seizures (NEDLAS).

Discussion: Our use of whole genome sequencing identified the fifth reported case of *CAPZA2*-related neurodevelopmental disorder. Fewer than 40 patients have been reported with NEDLAS, and we identified the fourth patient with the *AGO1* in-frame deletion p.Glu376del.

Conclusions: Whole genome sequencing can be effective in diagnosing patients with suspected genetic disorders despite negative standard of care clinical genetic testing and enables the practice of precision medicine.

INTRODUCTION

Over 26 million Americans are affected by rare genetic disorders, resulting in significantly higher annual health care costs than common conditions such as heart disease and cancer. Both pediatric and adult patients with rare diseases experience longer hospital stays, higher admission charges, increased readmissions, and elevated mortality rates compared to individuals with common conditions.[1] Rare diseases also remain the leading cause of infant mortality.[2] Intellectual disability (ID) and global developmental delay (GDD) are among the most frequently reported impairments in children, with GDD affecting 1% to 3% of children under the age of 5 and ID affecting 1.10% of children ages 3 to 17 years old.[3,4]

GDD is defined as significant delays in 2 or more developmental domains in children less than 5 years of age, while ID is defined as having significant limitations in both intellectual functioning and adaptive behavior.[5] Numerous testing routes can be pursued to determine the etiology of GDD/ID, including chromosomal microarray and whole exome sequencing, which are now standard-of-care tests ordered in outpatient clinics. A chromosomal microarray is a test that detects regions of genomic imbalances termed copy number variation. Whole exome sequencing involves sequencing the protein-coding regions of the genome. This "coding" portion of the genome is called the exome. The human exome represents < 2% of the genome but contains approximately 85% of known disease-related variants.[6] The diagnostic yield of chromosomal microarray in cases of GDD/ID ranges from 4.5% to 28.0% (median 13.7%), while the diagnostic yield of whole exome sequencing ranges from 28% to 43% (average 34%).[7] However, the majority of patients with GDD/ID remain undiagnosed after these evaluations, indicating the need for further work to provide specific diagnoses for these patients and families. The University of Wisconsin Undiagnosed Disease Program (UW UDP) employs whole genome sequencing to discover novel disease genes and variants to enable diagnoses of ultra-rare genetic

• • •

Author Affiliations: Center for Human Genomics and Precision Medicine, University of Wisconsin School of Medicine and Public Health (UW SMPH); Madison, Wisconsin (Heilmann, Hall, Meyn, Webb); Department of Pediatrics, UW SMPH, Madison, Wisconsin (Hall, Legare, Rice, Shao, Meyn, Webb); Gunderson Health System, LaCrosse Clinic, LaCrosse, Wisconsin (Rice); Department of Neurology, UW SMPH, Madison, Wisconsin (Seaborg); Biotechnology Center, UW – Madison; Madison, Wisconsin (Pavelec); Wisconsin State Laboratory of Hygiene; Madison, Wisconsin (Shao, Horner); Department of Pathology, UW SMPH; Madison, Wisconsin (Horner).

Corresponding Author: Bryn D. Webb, MD, 1111 Highland Ave, Office 2792, Madison, WI 53705; phone 608.262.2559; email bdwebb@wisc.edu; ORCID ID 0000-0001-6174-4677

disorders. We choose whole genome sequencing as a first-line test given that most referred patients already have had negative clinical whole exome sequencing, and a whole exome sequencing to whole genome sequencing approach leads to higher program costs. Here, we present 2 cases of suspected neurodevelopmental disorders of genetic etiology with negative clinical exome testing that we diagnosed using whole genome sequencing.

CASE PRESENTATIONS

Case 1

A 12-year-old male was referred to the UW UDP for neurodevelopmental concerns, including motor and speech delays and severe congenital hypotonia. He was born at 38 weeks gestation by emergency cesarean delivery due to fetal heart rate deceleration and failure to progress. At birth, he experienced breathing difficulties requiring supplemental oxygen and had a small right pneumothorax, which resolved spontaneously. His Wisconsin state newborn screen was normal. At 3 weeks of age, he presented to the emergency department with excessive vomiting and was diagnosed with pyloric stenosis, which was treated surgically. Between 7 and 10 months, he was hospitalized 4 times for respiratory infections exacerbated by hypotonia, making it difficult for him to clear his airway, and he was later diagnosed with early childhood asthma. At 10 months, At 10 months, he was identified to have significant developmental delays, achieving expressive language skills expected of a 3- to 4-month old, receptive language skills expected of an 8-month old, fine motor skills expected of a 4- to 5-month old, and gross motor skills expected of a 5-month old. At 12 months, his head circumference was measured at the 98th percentile (Z-score = 2.16). Magnetic resonance imaging (MRI) and head ultrasound revealed an incidental finding of a 3 mm cystic intradural lesion, but it was otherwise normal. At 14 months, a screening electrocardiogram showed sinus arrhythmia and findings of biventricular hypertrophy; however, an echocardiogram was normal. He was able to sit alone at 2 years and walk without help between 3 and 4 years. He was able to run at 9 years.

At 9 years and 6 months of age, moderate dilation of the ascending aorta was noted on echocardiogram (2.6 cm, Z-score = 4.3) with normal aortic root size. Follow-up echocardiogram at 12 years and 7 months revealed moderate dilation of the ascending aorta to similar degree (3.1 cm, Z-score = 4.2) with normal aortic root size. At 10 years old, the patient was diagnosed with autism after presenting with echolalia, repetitive verbalizations, and sensory-seeking behaviors. He also had thrombocytopenia identified consistently from age 19 months to 13 years, ranging from 75 K/uL to 145 K/uL and most often <120 K/uL.

Since age 12 years, the patient has used words in combination with a communication device to communicate. He is able to follow simple commands with a gesture. He is unable to walk long distances and uses a wheelchair or stroller. His physical exam at this time indicated weight of 34.5 kg (19.37%), height of 1.444 m (26.92%), and head circumference of 55.5 cm (88.03%).

At 13 years old, neurological exam revealed generalized hypotonia with decreased muscle bulk and size in biceps, triceps, quadriceps, soleus and gastrocnemius bilaterally. He has intrinsic hand muscles with decreased tone and bulk. He sits in a "W" position, and he is unable to rise from lying down to a seated position independently but can sit up from lying down with gentle assistance. He rises to stand from a seated position on the ground using ground and nearby structures to support himself in a modified Gower sign. He is not able to hold a squatting position. He has an intention tremor at reach in upper extremities bilaterally but no dysmetria. His upper extremity biceps and brachioradialis reflexes are 2+ and symmetric. His bilateral patellar reflexes are 1+, and he has a trace Achilles reflex bilaterally. He has a shuffling gait with limited plantarflexion and bilateral pronation at the ankles and knees.

Genetic testing for spinal muscular atrophy, myotonic dystrophy, Prader Willi, and Fragile X syndromes, as well as chromosomal microarray analysis, were negative. For metabolic evaluation, his acylcarnitine profile, plasma amino acids, urine organic acids, plasma and cerebrospinal fluid lactate and neurotransmitter profiles, and muscle biopsy for electron microscopy and mitochondrial depletion studies were normal. Whole exome sequencing completed in 2021 did not provide a definitive diagnosis, and the patient was referred to the UW UDP where whole genome sequencing was completed. For this sequencing, DNA was isolated from peripheral blood samples from the proband and mother; the father was unavailable for testing. Libraries were prepared and short-read, paired end, 150 base pair sequencing was obtained. FASTQ files were aligned to the human reference genome (GRCh38), and germline variant calling was performed using DRAGEN, which identifies single nucleotide variants, copy number variations, and structural variations. Variant calls were analyzed by the study team, which includes a board-certified clinical molecular geneticist. The team identified a disease-causing missense variant in *CAPZA2* c.776G>T; p.Arg259Leu, which was not inherited from the mother, and diagnosed the proband with *CAPZA2*-related disorder. See Case 1 discussion below for details.

Case 2

A 13-year-old male with global developmental delays, intellectual disability, seizures, and postnatal microcephaly was referred to the UW UDP. He was born at full term by normal spontaneous vaginal delivery after an uncomplicated pregnancy. After birth, he failed his newborn hearing screen twice and was diagnosed with mild bilateral sensorineural hearing loss at 2 months old. At 3 months, he was evaluated by genetics, who noted plagiocephaly, high-arched palate, minor ear anomalies, low hairline, umbilical hernia, and bilateral clubfoot. By 7 months, he developed postna-

Table 1. Clinical Features of All Known Individuals With CAPZA2-related Disorder

	UW UDP	Huang et al[9]		Pi et al[10]	Zhang et al[11]
	Case 1 Patient	Patient 1	Patient 2	Patient 1	Patient
Origin	European	Chinese	European	Chinese	ND
Variant	p.Arg259Leu	p.Arg259Leu	p.Lys256Glu	p.Arg260del	c.219+1G>A Splicing
Inheritance	Not inherited from mother, father unavailable	*de novo*	*de novo*	*de novo*	*de novo*
Gender	Male	Female	Female	Female	Male
Age	12 years	2.5 years	9 years	10 months	3 years
Growth					
Short stature	–	–	–	ND	–
Microcephaly	–; macrocephalic	–	–	+	–
Dysmorphic features	–	–	–	ND	ND
Development					
Speech delay	+	+	+	NA	–
Motor delay	+	+	+	+	–
Intellectual disability	+	NA	+	NA	+
Neurological					
Autism	+	NA	+	NA	–
Hypotonia	+	+	+	+	–
Seizure history	–	+; atypical febrile seizure	+; developed seizures at 7 months and infantile spasm occurred at 10 months	+; developed spasms at 3 months	+; 7 seizure episodes, 5 of which were febrile seizures
Magnetic resonance imaging abnormality	+; 3-mm cystic intradural lesion on spine	–	+; mild abnormal myelination in frontal area, mild perivascular space dilation in parietal and occipital area	–	+; septal pellucidum cyst and bilateral mastoiditis
Others					
Neonatal feeding difficulty	+	+	+	+	–
Additional findings	+; moderate dilation of ascending aorta; history of thrombocytopenia; pyloric stenosis; toe walking	–	+; hypopigmentation on right lower leg, hyper pigmentation upper legs; toe walking	–	–

Abbreviations: UW UPD, University of Wisconsin Undiagnosed Disease Program; +, feature present; –, feature absent; NA, not applicable due to patient age; ND, not determined.

tal microcephaly, with his head circumference measuring at the 1st percentile (Z-score = -2.10).

By 22 months, the patient had eye-rolling spells and was diagnosed with epilepsy after an electroencephalogram showed frequent occipital spike and wave discharges and severely abnormal background with absence of sustained posterior dominant rhythm and sleep architecture. At 26 months, head MRI showed mild delay in white matter myelination in the parietal and temporal regions bilaterally, prominence of the lateral and third ventricles, and simplification of the sulcal pattern along the sylvian fissures. He began walking at 4 years old and spoke his first word at 5 years old.

Repeat MRI at 7 years old showed similar configuration of brain morphology with interval maturation of the sulcation and myelination in both frontal and temporal lobes. T2/FLAIR signal abnormalities were seen in the periatrial white matter of both cerebral hemispheres with additional involvement of the subcortical white matter in both parietal lobes. At 11 years old, neurology noted focal seizures, choreoathetotic movements, truncal hypotonia with spasticity of the extremities, and an ataxic gait. Currently, at 13 years old, the patient has a happy demeanor, is largely nonverbal, and uses a walker.

Extensive genetic testing, including chromosome analysis, chromosomal microarray, connexin *GJB2* sequencing for hearing loss, and Prader-Willi methylation polymerase chain reaction, were negative. In 2021 at age 11 years, whole exome sequencing revealed a heterozygous pathogenic variant in the *ADSL* gene, which causes an autosomal recessive inborn error of metabolism; however, the patient is presumed to be unaffected as biallelic variants were not identified. In addition, he was identified to have a heterozygous, maternally inherited, likely pathogenic variant in *PTPRQ* (c.4015+1G>A). Pathogenic variants in *PTPRQ* are known to cause autosomal dominant or autosomal recessive hearing loss.[8] Notably, the mother has no history of hearing loss, and few families have been reported with disease. At age 13 years, whole genome sequencing by the UW UDP identified a de novo

Table 2. Clinical Features of Individuals With the de novo *AGO1* p.Glu376 Deletion Pathogenic Variant

	UW UDP	Schalk et al[16]		Niu et al[17]
	Case 2 Patient	Patient in Family 21	Patient in Family 22	Patient 1
Origin	African American/ European	European	ND	ND
Variant	p.Glu376del	p.Glu376del	p.Glu376del	p.Glu376del
Gender	Male	Male	Female	Female
Age	13 years	3 years	ND	ND
Growth				
Postnatal microcephaly	+	+	+	+
Dysmorphic features	+	+	ND	ND
Development				
Speech delay	+	+	+	+
Motor delay	+	+	–	+
Intellectual disability	+	+	+	+
Neurological				
Autism	–	–	+	ND
Hypotonia	+	+	+	+
Seizure history	+	+; generalized seizures with corpus callosotomy at age 7 secondary to intractable seizure	–	–
Abnormal movements	+	ND	+	–
Abnormal brain magnetic resonance imaging (MRI)	+; prominent ventricles, signal abnormality in the periatrial and subcortical white matter	–; normal MRI at 10 months	ND	+; myelin dysplasia, mild widening of bilateral frontotemporal space, and mild widening and deepening sulcus fissure
Others				
Neonatal feeding difficulty	+	–	–	+
Additional findings	+; Bilateral sensorineural hearing loss; bilateral club foot	–	–	+; Mild deafness

Abbreviations: UW UPD, University of Wisconsin Undiagnosed Disease Program; +, feature present; –, feature absent; ND, not determined.
[a]Schalk et al reported 33 individuals with NEDLAS including 2 patients with the same p.Glu376del variant.

in-frame deletion in *AGO1* (c.901_903delGAG; p.Glu376del), diagnosing him with neurodevelopmental disorder with language delay and behavioral abnormalities, with or without seizures (NEDLAS). See Case 2 discussion below for details.

DISCUSSION

The UW UDP's use of whole genome sequencing identified the fifth reported case of *CAPZA2*-related disorder and the fourth patient with the in-frame deletion p.Glu376del in *AGO1*, which causes NEDLAS.

Case 1

CAPZA2 encodes an F-actin capping protein, CapZ, which is critical for dendritic spine development and neurodevelopment. Capping proteins such as CapZ terminate the elongation of actin filaments by binding at the barbed end of the tentacle domain.[12] This regulation is essential for maintaining the proper length and stability of actin filaments, which are integral to the cytoskeleton and play a pivotal role in cellular morphology, motility, and various intracellular processes.[12,13] Knockdown of capping proteins α and β2 subunits in hippocampal cultures results in a marked decline in spine density, altered spine morphology, and a reduced number of functional synapses.[13] This suggests that *CAPZA2* significantly influences the function of capping proteins in dendritic spine development, thus playing a critical role in neurodevelopment. It is postulated that variants in or near the highly conserved basic residues of the *CAPZA2* tentacle domain disrupt the regulatory function of CapZ, contributing to the pathogenesis of neurodevelopmental disorders.[14]

The variant we identified in *CAPZA2* c.766G>T (p.Arg259Leu) previously has been reported as pathogenic in the literature, and this variant, along with the other 2 previously reported variants p.Lys256Glu and p.Arg260del, affect highly conserved basic residues.[9,10] According to American College of Medical Genetics and Genomics (ACMG) guidelines, this variant is classified as "likely pathogenic" (PS2, PM2, PP3, and PP5 criteria).[15] The identification finding of our patient with *CAPZA2*-related disease further confirms the known phenotype of this disease. Our patient shares features of speech and motor delays, hypotonia, and neonatal feeding difficulties with the previously reported patients (Table 1). Notably, our patient has not had any known seizures, unlike the

4 other reported patients. Additionally, our patient had pyloric stenosis, moderate dilation of the ascending aorta, and thrombocytopenia. As additional patients are identified, further exploration can determine whether these features are a part of the clinical spectrum of *CAPZA2*-related disease.

Case 2

AGO1 encodes Argonaute-1, a protein essential for gene silencing mediated by small non-coding RNAs. In transcriptional gene silencing, *AGO1* forms RNA-induced transcriptional silencing complexes that recruit chromatin-modifying proteins to create heterochromatin, thereby preventing mRNA synthesis. In post-transcriptional gene silencing, *AGO1* binds small RNAs, guiding them to complementary mRNA targets to induce mRNA degradation or inhibit translation.[18] Pathogenic variants in *AGO1*, including the p.Glu376del variant, are predicted to alter the flexibility of the *AGO1* linker domains, which likely impairs function in mRNA processing.[16] The variant identified in this patient is classified as "likely pathogenic" per ACMG guidelines (PS2, PM2, PM4, and PP5 criteria).[15]

Our patient is the fourth reported case with the same pathogenic variant p.Glu376del, and all 4 cases have postnatal microcephaly, GDD/ID, and hypotonia (Table 2).[16,17] Forty-six percent of patients with NEDLAS have variable brain MR anomalies, and 46% of affected individuals have a history of seizures.[16] Notably, our patient also has bilateral clubfoot and bilateral sensorineural hearing loss. Another patient with this variant also has mild deafness, potentially expanding the known clinical spectrum of disease.[17] However, it is also possible that the hearing loss is not directly caused by the *AGO1* variant but, instead, is secondary to the previously identified likely pathogenic variant in *PTPRQ*, which is known to be associated with hearing loss. Further investigation into the etiology of our patient's bilateral sensorineural hearing loss is warranted.

CONCLUSIONS

The UW UDP employs whole genome sequencing to diagnose Mendelian diseases in previously undiagnosed patients. Our identification of the fifth reported case of *CAPZA2*-related disorder and the fourth case of NEDLAS with the *AGO1* in-frame deletion p.Glu376del highlights the power of participation in research studies when clinical whole exome sequencing is unrevealing.

In Case 1, an in-depth exploration of the coding regions by our team identified a disease-causing variant that was not reported on clinical whole exome sequencing. In Case 2, the identification of a disease-causing variant was enhanced by new scientific literature published after clinical whole exome sequencing was completed, highlighting the crucial role of undiagnosed disease programs in reexamining challenging cases where prior clinical whole exome sequencing results were negative.

In general, the UW UDP performs whole genome sequencing as the first-tier test as: (1) patients are most often referred to our program following negative clinical whole exome sequencing, (2) it has superior mapping quality over whole exome sequencing,[19] and (3) it is more comprehensive in the ability to detect noncoding variants, large structural rearrangements, and copy number variation.[19,20]

Making a rare disease diagnosis reduces the uncertainty experienced by patients, families, and caregivers and may improve the overall quality of care. Integrating advanced genomic techniques and continuous reanalysis of genome data holds significant promise for improving diagnostics, patient care, and outcomes through more effective and personalized health care solutions. Our findings reinforce the importance of long-term follow-up for patients, including exome reanalysis or additional genomic testing through whole genome sequencing, to ensure ongoing diagnostic accuracy as new genetic insights and technologies emerge.

Funding/Support: None declared.

Financial Disclosures: None declared.

Acknowledgements: The authors extend their gratitude to the patients and their families who participated in this study.

REFERENCES

1. Navarrete-Opazo AA, Singh M, Tisdale A, Cutillo CM, Garrison SR. Can you hear us now? The impact of health-care utilization by rare disease patients in the United States. *Genet Med.* Nov 2021;23(11):2194-2201. doi:10.1038/s41436-021-01241-7

2. Ely DM, Driscoll AK. Infant mortality in the United States, 2020: data from the period linked birth/infant death file. *Natl Vital Stat Rep*. 2022;71(5):1-18.

3. Mithyantha R, Kneen R, McCann E, Gladstone M. Current evidence-based recommendations on investigating children with global developmental delay. *Arch Dis Child*. 2017;102(11):1071-1076. doi:10.1136/archdischild-2016-311271

4. Zablotsky B, Black LI, Maenner MJ, et al. Prevalence and trends of developmental disabilities among children in the United States: 2009-2017. *Pediatrics*. 2019;144(4):e20190811. doi:10.1542/peds.2019-0811

5. Vasudevan P, Suri M. A clinical approach to developmental delay and intellectual disability. *Clin Med (Lond).* 2017;17(6):558-561. doi:10.7861/clinmedicine.17-6-558

6. Bamshad MJ, Ng SB, Bigham AW, et al. Exome sequencing as a tool for Mendelian disease gene discovery. *Nat Rev Genet*. 2011;12(11):745-755. doi:10.1038/nrg3031

7. Savatt JM, Myers SM. Genetic testing in neurodevelopmental disorders. *Front Pediatr*. 2021;9:526779. doi:10.3389/fped.2021.526779

8. Eisenberger T, Di Donato N, Decker C, et al. A C-terminal nonsense mutation links PTPRQ with autosomal-dominant hearing loss, DFNA73. *Genet Med.* 2018;20(6):614-621. doi:10.1038/gim.2017.155

9. Huang Y, Mao X, van Jaarsveld RH, et al. Variants in CAPZA2, a member of an F-actin capping complex, cause intellectual disability and developmental delay. *Hum Mol Genet.* 2020;29(9):1537-1546. doi:10.1093/hmg/ddaa078

10. Pi S, Mao X, Long H, Wang H. A de novo inframe deletion variant in CAPZA2 tentacle domain with global developmental delay and secondary microcephaly. *Clin Genet.* 2022;102(4):355-356. doi:10.1111/cge.14186

11. Zhang XM, Xu KL, Kong JH, et al. Heterozygous CAPZA2 mutations cause global developmental delay, hypotonia with epilepsy: a case report and the literature review. *J Hum Genet.* 2024;69(5):197-203. doi:10.1038/s10038-024-01230-z

12. Akin O, Mullins RD. Capping protein increases the rate of actin-based motility by promoting filament nucleation by the Arp2/3 complex. *Cell*. 2008;133(5):841-851. doi:10.1016/j.cell.2008.04.011

13. Fan Y, Tang X, Vitriol E, Chen G, Zheng JQ. Actin capping protein is required for dendritic spine development and synapse formation. *J Neurosci.* 2011;31(28):10228-10233. doi:10.1523/JNEUROSCI.0115-11.2011

14. Kim T, Cooper JA, Sept D. The interaction of capping protein with the barbed end of the actin filament. *J Mol Biol.* 2010;404(5):794-802. doi:10.1016/j.jmb.2010.10.017

15. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med.* 2015;17(5):405-424. doi:10.1038/gim.2015.30

16. Schalk A, Cousin MA, Dsouza NR, et al. coding variants in the. *J Med Genet.* 2022;59(10):965-975. doi:10.1136/jmedgenet-2021-107751

17. Niu Y, Qian Q, Li J, et al. De novo variants in AGO1 recapitulate a heterogeneous neurodevelopmental disorder phenotype. *Clin Genet.* 2022;101(4):459-465. doi:10.1111/cge.14114

18. Janowski BA, Huffman KE, Schwartz JC, et al. Involvement of AGO1 and AGO2 in mammalian transcriptional silencing. *Nat Struct Mol Biol.* 2006;13(9):787-792. doi:10.1038/nsmb1140

19. Bagger FO, Borgwardt L, Jespersen AS, et al. Whole genome sequencing in clinical practice. *BMC Med Genomics.* 2024;17(1):39. doi:10.1186/s12920-024-01795-w

20. Brlek P, Bulić L, Bračić M, et al. Implementing whole genome sequencing (WGS) in clinical practice: advantages, challenges, and future perspectives. *Cells*. 2024;13(6):504. doi:10.3390/cells13060504

advancing the art & science of medicine in the midwest

WMJ

WMJ (ISSN 1098-1861) is published through a collaboration between The Medical College of Wisconsin and The University of Wisconsin School of Medicine and Public Health. The mission of *WMJ* is to provide an opportunity to publish original research, case reports, review articles, and essays about current medical and public health issues.

Visit www.wmjonline.org to learn more.