Original Article

Early Results of the Persian Registry of Cardiovascular Disease/Congenital Heart Disease (PROVE/CHD) in Isfahan

Ali Reza Ahmadi, MD[1], Mohammad Reza Sabri, MD[1], Zohreh Sadat Navabi, MSc[1*], Mehdi Ghaderian, MD[1], Bahar Dehghan, MD[1], Chehreh Mahdavi, MD[1], Somaieh Khodarahmi, MSc[2]

[1]*Pediatric Cardiovascular Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran.*
[2]*Isfahan Cardiovascular Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran.*

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Abstract

Background: *In 2016, a prospective registry for pediatric patients with congenital heart disease (CHD) was established in Isfahan, Iran. Data on pediatric CHD in Iran are scant; accordingly, we aimed to report the early results of the Persian Registry Of cardioVascular diseasE (PROVE/CHD) Registry in Isfahan.*

Methods: *All patients with CHD and associated defects diagnosed by pediatric cardiologists were assessed via echocardiography for inclusion in the present study between late 2016 and August 2019. The participants' sociodemographic characteristics, maternal history, birth history, medical history, current clinical presentations in the clinic or hospital, paraclinical data, cardiac diagnoses based on the International Classification of Diseases, 10th Revision (ICD-10), disease management plans, and medications were entered into a questionnaire by the subjects' parents/legal custodians and physicians and then transferred to the PROVE/CHD Registry.*

Results: *The PROVE/CHD registry encompasses 1252 patients with CHD (49.9% male) at a mean age of 6.50±6.36 years. The most frequent cardiac diagnoses were ventricular septal defect (39.3%), atrial septal defect (29.7%), patent ductus arteriosus (25.4%), pulmonary stenosis (11.0%), tetralogy of Fallot (6.1%), coarctation of the aorta (5.4%), and aortic stenosis (5.1%), respectively. The most frequent interventions were patent ductus arteriosus closure (4.3%), atrial septal defect closure (3.6%), pulmonary valvuloplasty (2.2%), coarctation of the aorta angioplasty (1.9%), and ventricular septal defect closure (1.1%), correspondingly. The approximate corresponding rates of corrective and palliative surgeries were 32.0% and 13.1%. The corrective surgeries were mainly comprised of ventricular septal defect closure (7.8%), patent ductus arteriosus closure (7.3%), atrial septal defect closure (5.1%), and tetralogy of Fallot repair (3.8%), respectively. The palliative surgeries mainly consisted of the Glenn shunt (9.0%) and pulmonary artery banding (3.6%).*

Conclusion: *The PROVE/CHD Registry collects data on pediatric patients with CHD. The results of this registry can provide epidemiological data and a set of homogeneously defined cases for further studies.*

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[*]**Corresponding Author:** ***Zohreh Sadat Navabi,*** *Pediatric Cardiovascular Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran. Tel: +98 031 36115212. Fax: +98 031 36115303. E-mail: zs.navabi@ gmail.com.*

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Introduction

Congenital heart disease (CHD) is the leading cause of infant mortality among birth defects. The reported prevalence rate of CHD is approximately 4 to 10 per 1000 live births.[1] Various etiological factors have been identified; however, the exact reasons for these abnormalities have remained unclear. CHD is now believed to have multifactorial etiologies in the form of a combination of both environmental and genetic factors.[2] The early detection and use of new techniques in the surgical repair and treatment of CHD has dramatically improved patients' outcome, with the disease now deemed treatable with improved survival.[3, 4] Although interventions and surgical repair are beneficial to most patients with CHD and improve their quality of life, by no means has a "cure" been found yet.[5] Children with repaired complex CHD and with unrepaired cyanotic defects are at risk for long-term complications and mortality during adulthood.[6] It is well known that the identification of CHD risk factors, in conjunction with national registries and local data collection, is crucial.[7]

Iran lacks reliable data on CHD risk factors and long-term outcomes because of the absence of a large, national registry. To address this deficiency, the first registry program of CHD in Iran was begun in the Iranian city of Isfahan, in 2016, under the title of "The Persian Registry Of cardioVascular diseasE (PROVE/CHD).[8, 9] The objectives of the PROVE/CHD Registry are as follows: 1) to define the incidence of CHD in the city of Isfahan in 5 outpatient clinics (2 private clinics and 3 university outpatient clinics), 2) to determine the known risk factors of CHD, 3) to enhance the quality of care, and 4) to pilot register patients with CHD and determine problems regarding further national CHD registrations.

This registry is the first national CHD registry in Iran and is almost unique among Middle Eastern countries. This paper is a report of the early results of the PROVE/CHD Registry in Isfahan.

Methods

PROVE/CHD is a registry of data on patients with CHD from 5 outpatient clinics (2 private and 3 university clinics) in the Iranian city of Isfahan. The data used in this study were collected between late 2016 and August 2019. The study protocol was approved by the Ethics committee of Isfahan University of Medical Sciences (Code: IR.MUI.MED.RED.1398.085).

A questionnaire was designed by pediatric cardiologists and validated by the institutional quality control committee experts. The questionnaire consisted of 7 different sections collecting information on demographic characteristics (eg, National Identity Number, registry location, parents' occupation, and family history of CHD), birth history (eg, birth condition and birth weight), maternal history (eg, registry location, history of diseases, addictions, medications during pregnancy, and exposure to chemical substances and X-ray during pregnancy), medical history (eg, time of first CHD diagnosis, genetic congenital abnormalities, and history of cardiac catheterization, cardiac surgery, and medications), current clinical presentations in the clinic or hospital (eg, height, weight, and associated diseases),[5] paraclinical data (eg, electrocardiography, chest X-ray, echocardiography, angiography, computed tomography angiography, and cardiovascular magnetic resonance imaging),[6] cardiac diagnosis (based on the International Classification of Diseases, 10th Revision [ICD-10]),[7] and disease management plans.

The children's parents/legal custodians received comprehensive explanations about the objectives of the registry so that informed consent could be obtained for the commencement of data collection. The PROVE/CHD questionnaires were completed by parents/legal custodians and physicians, and the information of the patients was confirmed by pediatric cardiologists. The data were thereafter transferred to the PROVE/CHD Registry.

The inclusion criteria consisted of all patients with CHD diagnosed by pediatric cardiologists and confirmed via echocardiography in 3 state-run outpatient pediatric cardiology clinics and 2 private outpatient pediatric cardiology clinics. Patients were excluded if they had a diagnosis of mitral valve prolapse or a patent foramen ovale.

During the 3-year period (ie, 2016 to 2019), data collection was performed in 1252 pediatric patients with CHD. The data were subsequently processed and analyzed using the SPSS software, version 23.0 (IBM Corp, Armonk, NY, USA). The qualitative variables were presented as frequencies and percentages, and the quantitative variables were expressed as the mean ± the standard deviation.

Results

From late 2016 to August 2019, the registry enrolled 1252 patients, of whom 625 (49.9%) were male. There were 292 (23.3%) neonates, 301 (24.0%) infants, 299 (23.9%) patients between 3 and 6 years old, 314 (25.1%) patients aged between 7 and 18 years, and only 46 (3.7%) patients aged

above 18 years.

Among the 1252 patients, 275 (22.0%) had low birth weights (<2500 g), 959 (76.5%) had appropriate weights for gestational age (2500–4000 g), and 18 (1.4%) were large for gestational age (>4000 g). The mother's age in 843 (67.4%) patients was between 18 and 35 years. In regard to parents' occupation, 1136 (90.7%) patients had homemaking mothers, and the fathers of 456 (36.4%) patients were workers (Table 1).

Table 1. Sociodemographic characteristics of the participants*

Sex	
Male	625 (49.9)
Female	627 (50.1)
Age of the Patients	
<1 mon	292 (23.3)
1 mon to 2 y	301 (24.0)
2–6 y	299 (23.9)
6–18 y	314 (25.1)
>18 y	46 (3.7)
Birth Weight of the Patients	
SGA (<2500 g)	275 (22.0)
AGA (2500–4000 g)	959 (76.6)
LGA (>4000 g)	18 (1.4)
Age of the Mother (y)	
<18 y	4 (0.3)
18–35 y	843 (67.4)
>35 y	405 (32.3)
Mother's Occupation	
Homemaker	1136 (90.7)
Employee	99 (8.0)
Worker	3 (0.2)
Other	14 (1.1)
Father's Occupation	
Laborer	456 (36.4)
Self-employed	238 (19.0)
Employee	209 (16.6)
Urban driver	73 (5.9)
Suburban driver	46 (3.7)
Jobless	41 (3.3)
Retired	20 (1.6)
Other	169 (13.5)
Birth Place	
Isfahan Province	1017 (81.2)
Another Province	235 (18.7)

*Data are presented as n (%).
SGA, Small for gestational age; AGA, Appropriate for gestational age; LGA, Large for gestational age

The results showed that the parents of 31.6% of the study population had consanguineous marriages. Of all the diseases investigated among the patients' mothers, hypothyroidism (n=106, 8.5%) and diabetes mellitus (n=48, 3.8%) were the most common. These mothers used levothyroxine and metformin, respectively.

A total of 1252 (4.0%) patients had CHD associated with syndromes. For instance, 44 (3.5%) patients had Down syndrome. The time of first CHD diagnosis in 621 (49.6%) patients was in the neonatal period. Cardiac murmurs were auscultated in 1121 (89.5%) patients, and respiratory distress was reported in 86 (6.8%) patients in the physical examinations (Table 2).

Table 2. Baseline characteristics of the participants*

Consanguineous Marriages	
No relation	857 (68.4)
Third-degree relation	284 (22.7)
Fourth-degree relation	111 (8.9)
Maternal Illness During Pregnancy	
Hypothyroidism	106 (8.5)
Diabetes mellitus	48 (3.8)
Hypertension	21 (1.7)
Syndromes	
Down syndrome (Trisomy 21)	44 (3.5)
Williams syndrome	3 (0.2)
Turner syndrome	2 (0.1)
Marfan syndrome	1 (0.0)
Time of CHD Diagnosis	
Prenatal	34 (2.8)
Neonatal	621 (49.6)
Infancy	352 (28.1)
Toddlerhood	101 (8.1)
Childhood	106 (8.5)
Adolescence	21 (1.6)
Adulthood	17 (1.3)
Clinical Findings in CHD (data of the first examination)	
Murmur	1121 (89.5)
Respiratory distress	86 (6.8)
Pulmonary hypertension	70 (5.5)
Cyanosis	64 (5.1)
Asymptomatic	59 (4.7)

*Data are presented as n (%).
CHD, Congenital heart disease

With respect to CHD lesions, 765 (61.1%) patients had a single lesion, while 487 (38.8%) had more than 1 lesion. CHD subtypes were classified in 4 categories: 1) acyanotic with left-to-right shunts (n=1206, 96.3%), 2) obstructive (n=275, 21.9%), 3) cyanotic with decreased pulmonary flow (n=110, 8.7%), and 4) cyanotic with increased pulmonary flow (n=29, 2.3%). Table 3 presents the list of CHD subtypes.

The most frequent main cardiac diagnoses were ventricular septal defect (VSD) (n=493, 39.3%), atrial septal defect (ASD) (n=372, 29.7%), patent ductus arteriosus (PDA) (n=318, 25.4%), pulmonary stenosis (n=138, 11.0%), tetralogy of Fallot (ToF) (n=76, 6.1%), coarctation of the aorta (CoA) (n=68, 5.4%), and aortic stenosis (n=64, 5.1%). Regarding CHD subtypes, ASD and PDA were more frequent in female patients, whereas VSD, pulmonary stenosis, ToF, aortic stenoses, and CoA predominated in males (Figure 1). The CHD diagnosis was coded based on the ICD-10 (sections Q20–Q26) (Table 4).

Table 3. Congenital heart defects subtypes in the PROVE/CHD Registry*

Single Lesions	765 (61.0)
Multiple Lesions (n=487)	
Two	304 (24.3)
Three	120 (9.6)
Four	41 (3.3)
Five	17 (1.4)
Six	5 (0.4)
Acyanotic Lesions	
Left-to-right shunt (n=1206)	
Ventricular septal defect	493 (39.3)
Atrial septal defect	372 (29.7)
Patent ductus arteriosus	318 (25.4)
Atrioventricular septal defect	23 (1.8)
Obstructive Lesions (n=275)	
Aortic stenosis	69 (5.5)
Pulmonary valve stenosis	138 (11.0)
Coarctation of the aorta	68 (5.4)
Cyanotic Lesions	
Decreased pulmonary flow (n=110)	
Tetralogy of Fallot	76 (6.1)
Pulmonary atresia	32 (2.6)
Tricuspid atresia	2 (0.2)
Increased pulmonary flow (n=29)	
Transposition of the great arteries	18 (1.4)
Total anomalous pulmonary venous return	11 (0.9)

*Data are presented as n (%).
There were some lesions of CHD (eg, acyanotic and cyanotic) in a single patient simultaneously.

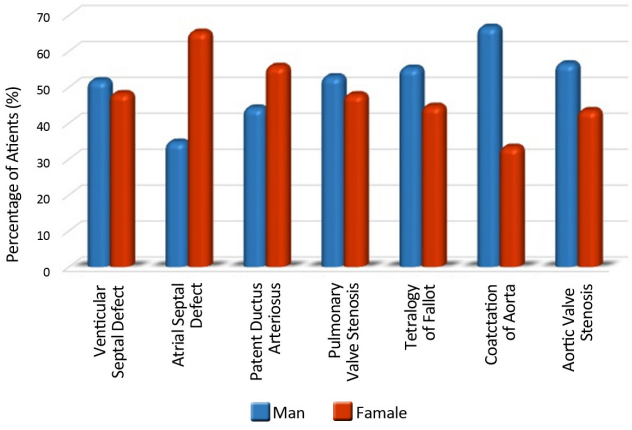

Figure 1. Sex distribution of the most common congenital heart diseases

There was a history of previous medication use for heart failure (21.0%), anticoagulation (7.3%), treatment for pulmonary hypertension (4.6%), and antiarrhythmic drugs (1.3%).

A total of 229 (18.2%) patients had congenital catheterization, and 185 (14.7%) patients had interventional catheterization. Additionally, 351 (28%) patients had 1 cardiac catheterization, 39 (3.1%) had 2 cardiac catheterizations, and

Table 4. Cardiac diagnoses based on the ICD-10 (Sections Q20–Q26) for the patients with CHD*

Q20.Chambers and Connections		Congenital mitral stenosis	8 (0.6)
Double-outlet right ventricle	14 (1.1)	Congenital mitral insufficiency	8 (0.6)
Double-outlet left ventricle	1 (0.1)	Hypoplastic left heart syndrome	1 (0.1)
Discordant ventriculoarterial connection	18 (1.4)	Other cardiac malformations of the aorta and the mitral valve	15 (1.2)
Double-inlet ventricle	1 (0.1)	Cardiac malformations of the aorta and the mitral valve, Unspecified	14 (1.1)
Discordant atrioventricular connection	3 (0.2)	Q24. Other Congenital Malformations of the Heart	
Isomerism of atrial appendages	2 (0.2)	Dextrocardia	10 (0.8)
Other	3 (0.2)	Pulmonary infundibular stenosis	4 (0.3)
Unspecified	33 (2.6)	Other specified cardiac malformations of the heart, Unspecified	10 (0.8)
Q21.Cardiac Septa		Malformations of the heart, Unspecified	11 (0.9)
Ventricular septal defect	493 (39.3)	Q25. Great Arteries	
Atrial septal defect	372 (29.7)	Patent ductus arteriosus	318 (25.4)
Atrioventricular septal defect	23 (1.8)	Coarctation of the aorta	68 (5.4)
Tetralogy of Fallot	76 (6.1)	Supravalvular aortic stenosis	5 (0.4)
Other malformations of the cardiac septa	8 (0.6)	Other cardiac malformation of the aorta	4 (0.3)
Malformation of the cardiac septum, Unspecified	19 (1.5)	Atresia of the pulmonary artery	2 (0.2)
Q22. Pulmonary and Tricuspid Valves		Coarctation of the pulmonary artery	2 (0.2)
Pulmonary valve atresia	32 (2.6)	Congenital pulmonary arteriovenous malformations	1 (0.1)
Congenital pulmonary valve stenosis	138 (11.0)	Malformations of the great arteries, Unspecified	3 (0.2)
Other congenital pulmonary valve insufficiencies	2 (0.2)	Q26. Great Veins	
Congenital tricuspid stenosis	3 (0.2)	Total anomalous pulmonary venous return	11 (0.9)
Hypoplastic right heart	2 (0.2)	Partial anomalous pulmonary venous connection	7 (0.6)
Other congenital malformations of the tricuspid valve	5 (0.4)	Other cardiac malformations of the great veins	12 (1.0)
Q23. Aortic and Mitral Valves		Malformations of the great veins, Unspecified	11 (0.9)
Congenital stenosis of the aortic valve	64 (5.1)		
Congenital insufficiency of the aortic valve	16 (1.3)		

*Data are presented as n (%).
ICD-10, International Classification of Diseases, 10th; CHD, Congenital heart

10 (2.4%) had 3 or more cardiac catheterizations. The most frequent interventions were PDA closure (4.3%), ASD closure (3.6%), pulmonary valvuloplasty (2.2%), CoA angioplasty (1.9%), and VSD closure (1.1%), correspondingly.

Corrective surgeries were performed on 401 (32.0%) patients and palliative surgeries on 165 (13.1%). Further, 291 (23.2%) patients had 1 surgery, 54 (4.3%) patients had 2 surgeries, and 14 (3.7%) patients had 3 or more surgeries. The most frequent corrective surgeries were VSD closure (7.8%), PDA closure (7.3%), ASD closure (5.1%), and ToF repair (3.8%), respectively. The most frequent palliative surgery was the Glenn shunt (9.0%), followed by pulmonary artery banding (3.6%). Table 5 lists the cardiac medications, the most frequent interventions, and corrective and palliative surgeries.

Table 5. Medications and different cardiac procedures of the patients*

Heart Failure (n=264)	
Furosemide	88 (7.0)
Captopril	83 (6.6)
Digoxin	71 (5.7)
Spironolactone	22 (1.8)
Anticoagulants (n=92)	
Acetylsalicylic acid	58 (4.6)
Warfarin	18 (1.4)
Plavix	16 (1.3)
Treatment for Pulmonary Hypertension (n=58)	
Sildenafil	49 (3.9)
Tadalafil	5 (0.4)
Bosentan	4 (0.3)
Antiarrhythmics (n=17)	
Propranolol	12 (0.1)
Amiodarone	4 (0.3)
Sotalol	1 (0.1)
Cardiac Procedures	
Congenital Catheterization	229 (18.2)
Interventional Catheterization (n=185)	
PDA closure	55 (4.3)
ASD closure	46 (3.6)
Pulmonary valvuloplasty	28 (2.2)
CoA angioplasty	25 (1.9)
VSD closure	13 (1.1)
Other	18 (1.4)
Corrective surgery (n=401)	
VSD closure	98 (7.8)
PDA closure	92 (7.3)
ASD closure	65 (5.1)
ToF repair	48 (3.8)
COA repair	22 (1.7)
PS repair	18 (1.4)
Other	58 (4.6)
Palliative surgery (n=165)	
Glenn shunt	113 (9.0)
PA banding	46 (3.6)
Other	6 (0.4)

*Data are presented as numbers (%).
ASD, Atrial septal defect; VSD, Ventricular septal defect; PDA, Patent ductus arteriosus; ToF, Tetralogy of Fallot; CoA, Coarctation of the aorta; PS, Pulmonary stenosis; PA, Pulmonary atresia

Discussion

In the first Iranian registry of CHD, which was initiated in the city of Isfahan in 2016, within 3 years, 1252 patients with CHD were registered.

In this study, 275 (21.8%) pediatric patients with CHD had a birth weight of less than 2500 g, and 405 (32.3%) mothers were aged above 45 years. Previous research has shown that birth weight and maternal age during pregnancy can meaningfully increase the risk of CHD.[10, 11] According to our results, the parents of 395 (31.6%) of our pediatric patients were consanguineously married. There is a substantial body of evidence indicating the existence of a relationship between consanguineous parents and congenital defects.[12] Hypothyroidism (8.5%) and diabetes mellitus (3.8%) were the most common diseases during pregnancy in our investigation, which is consistent with a large number of studies confirming the association between maternal diseases in pregnancy and CHD such as those conducted by Grattan et al,[13] Pastor-García et al,[14] and Ahmadi et al.[15]

CHD has a significant association with Down syndrome.[16, 17] The data analysis in the current study revealed that 44 (3.5%) patients with CHD had Down syndrome.

In our study, only 2.8% of the patients were diagnosed prenatally; this rate is lower than the European average of 25.5%.[4, 14] Better devised professional education programs for prenatal sonographers can increase the prenatal diagnosis of CHD.[18] The time of the first CHD diagnosis in 49.6% of our study population was in the neonatal period, compared with 17.1% in Pakistan and 24.9% in Saudi Arabia.[19, 20]

Since almost half of deaths from CHD occur in infancy and some untreated patients with CHD do not survive their first year, the early detection and correction of CHD during the first year of life is vitally important.[21, 22]

Heart murmurs were detected in 1121 (89.5%) of our patients. According to Mirzarahimi et al,[23] 51.6% of the neonates with cardiac murmurs in their investigation had CHD.

In the current study, 765 (61.1%) patients had only a single lesion, and the acyanotic type of CHD was more frequent than the cyanotic type. In terms of obstructive lesions, left-to-right shunting was the most frequent (96.3%) lesion. Cyanotic CHD with decreased pulmonary flow was more frequent than lesions with increased pulmonary blood flow. This finding is in agreement with the results of Yanji et al[24] in China, Pastor et al[14] in Spain, and Calzolari et al[25] in Italy.

The most frequent subtypes of CHD based on the ICD-10 codes were VSD, ASD, PDA, pulmonary valve stenoses, ToF, CoA, and aortic valve stenoses. Many CHD registries in other countries have reported similar results concerning the frequency of CHD types; that is, VSD and ASD comprise the most frequent types of CHD.[14, 25, 26] In the Québec Registry, VSD and ASD had the highest prevalence, which is compatible with the current study. In contrast, in

the CONCOR Registry, ToF was demonstrated as the most prevalent main diagnosis.[7, 27] A possible explanation for this difference may be the age of the registered population and the role of environmental and genetic factors. Some instances of CHD such as VSD tend to close spontaneously in the first years of life; accordingly, studies with a later registration age do not include this item in their registration.

In our study, a history of treatment with cardiac medications for heart failure was reported in 264 (21.0%) subjects. The most frequently consumed drugs were furosemide (7.0%) and captopril (6.6%). Additionally, anticoagulants, medications for pulmonary hypertension, and antiarrhythmic medications were consumed by 92 (7.3%), 58 (4.6%), and 17 (1.3%) patients, respectively. In 2 registries of patients with adult CHD, the consumption of antiarrhythmic medications was reported in 15.0% of the subjects in the CHALLENGE Registry and 18.0% of the subjects in the CONCOR Registry.[28, 29]

In our study, 229 (18.2%) patients underwent congenital catheterization and 185 (14.7%) had interventional catheterization. Moreover, 401 (≈32.0%) patients had corrective surgeries and 165 (13.1%) had palliative surgeries.

The most frequent interventions in this study were PDA and ASD closure. The rate of VSD closure was lower because of the frequency of PDA and ASD in our population and the accessibility of devices for their closure in our center.

Previous studies have shown that major developments in the diagnosis of complex CHD, in tandem with its medical care, treatment options, surgical techniques, and postoperative care, have conferred decreased morbidity and mortality and enhanced quality of life in children with CHD.[14, 30]

To our knowledge, the PROVE/CHD Registry is the first of its kind for patients with pediatric CHD in Iran and the Middle East. In addition, this study is a part of limited registration studies in the entire world on pediatric CHD that aim to provide epidemiological data and a set of homogeneously defined cases for further studies. However, there are some limitations to our study. Most of the patients enrolled in this registry were those referred to pediatric cardiologists in private clinics and university outpatient clinics, but not all children with a congenital heart defect from birth. Therefore, some of the results of the current study such as the prevalence of congenital heart defects cannot be generalized to the general population of Iran.

Conclusion

The registration of pediatric patients with congenital heart disease in the Iranian city of Isfahan can provide a valuable data pool with a view not only to improving management, prevention, and treatment plans but also to contributing to local, national, and international research.

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