KNOWLEDGE AND ATTITUDES TOWARDS AUTISM SPECTRUM DISORDERS AMONGST GENERAL PRACTITIONERS IN KARACHI, PAKISTAN

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ABSTRACT

KNOWLEDGE AND ATTITUDES TOWARDS AUTISM SPECTRUM DISORDERS AMONGST GENERAL PRACTITIONERS IN KARACHI, PAKISTAN

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Introduction: Autism Spectrum Disorder (ASD) is a complex lifelong neurodevelopmental and behavioral disorder that manifests in infancy or early childhood and is characterized by impairments in social interaction and communication, and by repetitive, stereotyped behavior. While the diagnosed prevalence of ASD is on the rise, reliable epidemiological data, including risk factors for ASD is lacking in many developing countries, including Pakistan. In this context, the main objective of this study is to evaluate whether there is a lag in information transfer between what is known about ASD in developed countries compared to that which is known amongst general practitioners (GP) in Karachi, Pakistan. More specifically, this research tests the following two hypotheses: (1) Physicians younger than 30 years of age are more likely to have knowledge of ASD, and (2) Among general practitioners who self-reported having an understanding of ASD, when questioned about old and new theories, those that graduated in the distant past (before 1990), will continue to hold antiquated misconceptions regarding ASD diagnosis and treatment. **Methods:** We utilized the Mediguide Comprehensive Medical Directory to establish a sampling frame for the city of Karachi (n = 5,849 practicing general practitioners), from which a final analytic sample of 348 physicians was derived. We used the statistical software, SAS® Version 9.4, for all analyses. **Results:** Of 348 physicians, 148 (44.6%) had heard of the term “autism.” Physicians younger than 30 years of age were more likely to self-report knowledge of autism compared to physicians who were older than 50 years of age

(OR = 2.30; 95% Cl: 1.17, 4.55). During their medical school training, physicians who had ward rotations in pediatrics and internal medicine were more likely to self-report knowledge of autism (OR = 2.36; 95% Cl: 1.38, 4.03 and OR = 2.37 95% Cl: 1.31, 4.28), respectively. Physicians who graduated after 1990 were 4.28 times more likely to correctly respond to five or more of the eight questions regarding diagnosis and treatment of autism (OR = 4.28; 95% Cl: 1.00, 21.37). **Discussion:** This study adds to what is currently known about the knowledge disparity with respect to ASD that exists between developed countries and Karachi, Pakistan. As the global prevalence of ASD becomes a major public health concern, narrowing this knowledge gap takes on an increasingly important significance. It is imperative that general practitioners in Karachi gain a contemporary understanding of ASD so that timely interventions can be implemented.

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KEY TO ABBREVIATIONS

AIC	Akaike Information Criterion
ASD	Autism Spectrum Disorder
COS	Childhood Onset Schizophrenia
GPs	General Practitioners
MSUIRB	Michigan State University Institutional Review Board
PPV	Positive Predictive Value
SC	Schwarz Criterion
SCQ	Social Communication Questionnaire
SRS-2	Social Responsiveness Scale™, 2nd Edition

Introduction

Autism Spectrum Disorder (ASD) is a complex lifelong neurodevelopmental and behavioral disorder that manifests in infancy or early childhood. It is characterized by impairments in social interaction and communication, and by repetitive, stereotyped behavior (Tchaconas and Adesman 2013). The diagnosed prevalence of ASD is on the rise in developed countries and has become a major public health concern (Matson and Kozlowski 2011, Baxter, Brugha et al. 2015). In these countries, resources have been invested to accurately assess prevalence and identify potentially related risk factors (Zwicker and Emery 2014).

At the time of this study, reliable epidemiologic data on ASD were lacking in Pakistan. In most developing countries, the prevalence of factors associated with ASD are unknown (Daley 2002). To best understand how healthcare for ASD is delivered in Pakistan, we need to get a better understanding of Pakistani physician's knowledge and views about ASD (Imran and Azeem 2014). As the first step in conducting population based epidemiological studies in Pakistan we proposed the Pakistan Autism Project. This project set out to administer a questionnaire to assess knowledge, attitudes, and practices of the General Practitioners (GPs) in Karachi, the largest city in Pakistan.

The primary objective of this study is to evaluate whether there is a lag in information transfer between what is known about ASD in developed countries compared to that which is known by general practitioners in Karachi. Secondly, to assess the effectiveness of continuing medical education amongst practicing physicians to keep up-to-date with ASD research. The following two hypotheses are tested to achieve this overarching goal: (1) Physicians who

graduated from medical school more than 20 years ago lack a contemporary understanding of ASD, and (2) Some physicians who self-report knowledge of ASD might still be unqualified to treat their patients presenting with ASD and to properly refer them to appropriate care.

Specific *Aims*

1. To assess the knowledge, attitude and practices of the general practitioners as it pertains to ASD in Karachi
2. To identify factors associated with knowledge, attitude and practices of the general practitioners in Karachi regarding ASD

Chapter 1. Background

This introduction to the topic of ASD is distributed amongst two chapters: *Chapter 1* will start with a brief history of ASD, standardized diagnostic criteria, and treatment options for people with ASD. *Chapter 2* focuses on the global burden of disease for ASD with a focus on the developing world.

Later in *Chapter 1*, I will also present the most current research findings in regards to ASD risk factors, surveillance, and the latest treatment options. Although, comparatively little has been written regarding the impact of ASD in developing countries *Chapter 2* will compare and contrast the efforts of researchers and policymakers in the developing world and in industrialized nations.

This historical perspective on ASD provides context for questions presented in the questionnaire we administered to study subjects. **To best assess the knowledge of physicians surveyed, I asked them questions to confirm or dispel old and new theories regarding ASD.** In *Chapter 3*, I will present the study design and explain how the sampling frame was established to derive our study sample from this population. I also present the methods of the developing the questionnaire design and flow. Then, *Chapter 4*, I present the statistical methods for analysis and the results that follow. *Chapter 5* provides the discussion of our findings in the context of existing literature and the implications of our research for the clinical knowledgebase.

1.1 Historical Perspective

Although, we have known of autism as a developmental disorder for more than half a century, in a large part, ASD research remains in the descriptive stages of epidemiological studies. The term “autism” was first used by Eugen Bleuler a Swiss psychiatrist in 1911 to describe aloneness and ambivalence in adult schizophrenia. Almost a century later, this misconception in diagnostic clarity between ASD and Schizophrenia remains difficult to disabuse (Woodbury-Smith, Boyd et al. 2010).

In 1943, Dr. Leo Kanner was first to publish a detailed description of autism as it is known today. Dr. Kanner’s article “Autistic Disturbances of Affective Contact” was based on a case study of eleven children compiled over five years (Kanner 1943). Kanner’s study subjects were children who had withdrawn human contact since the age of one. He noted detailed descriptions of many aspects of these children’s lives. He observed their interpersonal interactions, development since early childhood, and even eccentric habits specific to each child. Kanner observed five distinguishing criteria for autistic children; a lack of contact with other people, strong desire for “preservation of sameness,” a fascination with specific objects typically used for repetitive activities, language development not used for interpersonal communication, and “the retention of intelligent and pensive physiognomy and good cognitive potential” (Eisenberg and Kanner 1956).

Seven decades later, there is scientific consensus “that autism occurs equitably across demographic groups” and ASD does not have racial, ethnic or social boundaries (Dyches 2004). In contrast, in 1943, when Kanner described his study sample and presented his patients with ASD symptomology, he noted that every child in his observation “[came] of highly intelligent

families" (Kanner 1943). Furthermore, he described his patients coming from households of intelligent families who were "strongly preoccupied with scientific, literary, or artistic work" (Kanner 1943). These statements lead to much controversy decades into the future (Dyches 2004).

Just a year after Leo Kanner's original publication, an Austrian pediatrician, Hans Asperger published an article titled "Autistic Psychopathy in Childhood", describing "autistic psychopathy" in four children (Asperger 1944). Both Kanner and Asperger made similar observations in their patients but Asperger's patients all developed speech before school age, while only one of Kanner's patients developed speech (Frith 1991). Dr. Asperger referred to his patients with autistic psychopathy as "little professors" and they were described as "talking like grown-ups" even in early childhood (Asperger 1944, Frith 1991).

Both Kanner and Asperger noted that patients with these behavioral traits had previously been misdiagnosed as either schizophrenic or feeble-minded (Kanner 1943, Asperger 1944). As Kanner explained, "several children of our group were introduced to us as idiots or imbeciles. One still resides in a state school for the feebleminded, and two had been previously considered as schizophrenic" (Kanner 1943).

Before DSM-III, many childhood disorders such as autism, schizophrenia, and several other severe mental disorders were categorized together in clinical practices (American Psychiatric Association. 1980). The relationship between autistic disorder and childhood onset schizophrenia (COS) has evolved during the last decade (Reaven, Hepburn et al. 2008). The establishment of a diagnostic criteria was important in distinguishing between COS and ASD. Kolvin emphasizes that in the middle of the 20th century the lack of uniformity in diagnostic

criteria resulted in several childhood onset psychoses to be muddled together (Kolvin 1971). In exploratory studies, it was observed that psychotic disorders are dependent on age when symptoms emerge. Infantile autism was among other psychoses that were observed within the first two years after birth (Kolvin 1971). Kanner in his groundbreaking paper pointed out that late-onset psychoses, observed after three years of age more closely resembled adult schizophrenia (Kanner 1943, Kolvin 1971)

Age of onset and the frequency of occurrence of different symptoms have been two of the most common defining characteristics that set apart schizophrenia and autism in children (Kolvin 1971, Ghaziuddin 2005). Children with childhood onset schizophrenia present with hallucination and delusions, (Russell 1994) while autistic children typically have deficits in social interaction, imaginative play, social/ emotional reciprocity, and communication (American Psychiatric Association 1994). As the scientific community started to agree upon this set diagnostic criteria, the original association between COS and ASD was dispelled. Nearly 50 years ago, autism and COS started being distinctly defined (Kolvin 1971, Petty, Ornitz et al. 1984, Green, Padron-Gayol et al. 1992).

1.2 Diagnosing Autism Spectrum Disorders

In 1980, infantile autism was first included in the *Diagnostic and Statistical Manual of Mental Health Disorders, Third Edition* (DSM-III), within the category of Pervasive Developmental Disorders. It wasn't until the revision of the DSM-III that Autistic Disorder was reclassified and was no longer just a contemporary classification. The clinical criteria for identifying ASD are defined in the *Diagnostic Statistical Manual of Mental Health Disorders, Fourth Edition* (DSM IV) and also the more recent *Diagnostic Statistical Manual of Mental*

Disorders, Fifth Edition (DSM-V) (American Psychiatric Association 1994, American Psychiatric Association 2000, American Psychiatric Association. and American Psychiatric Association. DSM-5 Task Force. 2013). According to these manuals, ASD encompasses three developmental disorders; Autistic disorder (AD), Asperger's Syndrome (AS) and Pervasive Developmental Disorders, Not Otherwise Specified (PDD-NOS). Although this study was conducted before the publication of DSM-V, the latest version of the diagnostic manual revises the criteria for autism, no longer includes Asperger's Syndrome, but includes a new diagnosis for social communication disorder (SCD) (American Psychiatric Association. and American Psychiatric Association. DSM-5 Task Force. 2013).

ASD are spectrum disorders and lie on a continuum extending from AS or mild social deficit to severe handicap. There is also a high level of variability with respect to the presence and intensity of symptoms (Johnson, Myers et al. 2007). It is suggested that due to such variability in symptoms there may be additional subtypes (Johnson, Myers et al. 2007). Each child is unique and their respective symptomology poses challenges in accurate diagnosis for ASD. There are no predictive pathognomonic features but early deficits in socialization are fairly reliable "red flags" (Johnson, Myers et al. 2007).

1.2.1 Autism Screening

Over the last few decades, there have been considerable advances in research to understand early behavioral markers that can accurately provide an ASD diagnosis (Zwaigenbaum, Bauman et al. 2015). Translation of these discoveries into clinical practice is dependent upon parents, primary care physicians and teachers being able to use simple screening tools to identify children who may be on the autism spectrum. Furthermore, the

broad implementation of these tools results in optimal detection of early signs in children that may lead to proper diagnosis (Johnson and Myers 2007). Children who receive an early diagnosis and early intervention show substantial improvement in development (Robins and Dumont-Mathieu 2006). If these children are able to develop language and symbolic play by the age of five, they tend to have a higher probability of being enrolled in a regular classroom (Robins and Dumont-Mathieu 2006).

ASD meet many of the World Health Organization's criteria for screening: the condition poses an important health care problem, there is treatment available for the ASD, there is an acceptable test available for the condition, and most importantly when treatment is initiated early on, the patient outcomes are more favorable (World Health Organization 2010). A good screening test should be easy to administer, inexpensive, accurate, and reliable. A screening test should also be sensitive.

Sensitivity and specificity for these screening instruments are the primary considerations as they get incorporated into practice. As a brief description, sensitivity of a screening instrument refers to how accurately an instrument can identify children on the autism spectrum when they are known to have ASD. Specificity, on the other hand, refers to how accurately a subject can be classified as normal when they truly don't have ASD. A more sensitive screening test results in fewer false negatives at the cost of more false positives. Taking into consideration that there is a cost associated with a false positive, a screening instrument's main purpose is to identify red flags for a clinician and therefore should have a higher sensitivity. From a clinician's perspective, another important consideration is positive predictive value (PPV); a screening test's PPV determines the probability that a subject has a

disease when a screening tests abnormally. The PPV is dependent on three things, the sensitivity, specificity, and prevalence of the disease. A disease with a very low prevalence will make the PPV small.

Screening instruments alert a child's caretaker to seek professional care and a confirmed diagnosis from a specialist. There are two general categories of ASD screening tools: level 1 screens apply to children regardless of risk status, while level 2 screening tools are designed for children who are at an increased risk for ASD (Johnson and Myers 2007). These screenings tools range from short checklists like the Checklist for Autism in Toddlers (M-CHAT) that can be administered by parents as both a level 1 screen or a level 2 screen (Robins, Fein et al. 2001) to the Social Communication Questionnaire (SCQ) which is more appropriate for the primary care setting (Allen, Silove et al. 2007). The Social Responsiveness Scale, 2nd Edition (SRS-2) is also commonly used to detect subtle symptoms associated with ASD and to identify social impairment such as social awareness, social cognition, and social communication (Constantino and Gruber 2012).

1.2.2 Standardized diagnostic instruments (ADI-R and ADOS)

At this point, there are no laboratory tests for diagnosing autism. The Diagnostic Statistical Manual of Mental Disorders (DSM) offers a standard criterion for diagnosing mental disorders. The DSM is published by the American Psychiatric Association and is updated based on updated scientific discoveries. The DSM-V provides mental health professionals with a diagnostic criteria to diagnose autism spectrum disorders. Most epidemiologic studies on ASD use the DSM criteria as the primary means to diagnose and identify autism although there is some controversy over its structure and exact definitions of mental disorders (Conner 1999).

Three characteristics symptoms that are commonly used to identify and define ASD include impairments in social interaction, verbal and nonverbal communication, and repetitive behaviors or interests.

In the last two decades, there has been dedicated attention to developing standardized instruments to accurately identify ASD cases at an early age. Two such instruments have become the most common in ASD research and clinical practice: the Autism Diagnostic Observation Schedule ADOS (Lord, Risi et al. 1999) and the Autism Diagnostic Interview – Revised ADI-R (Lord, Rutter et al. 1994). Along with clinical judgment, these instruments have received much acclaim and have become the gold standard for diagnosis and case ascertainment for autism research (de Bildt, Sytema et al. 2004). ADOS and ADI-R have also demonstrated accuracy in distinguishing between autism and missed developmental milestones in a child's development (Reaven, Hepburn et al. 2008).

The ADOS is a semi-structured, play based observational interview of patients who are suspected of having ASD. ADOS has four modules that are organized in tasks and materials appropriate for the patient's age and expressive language level. Observations during these modules are used to score the patient on their social and communication domains. ADI-R is also a semi-structured caregiver interview and it has algorithms scoring the patient in three domains; social reciprocity, communication, and repetitive behaviors. Both these instruments require substantial training and skill in administration and scoring.

1.3 Treatment

Although there is no cure for ASD, there are many treatment options for patients who have been diagnosed with ASD. Therapy and treatment for ASD are very intensive and

comprehensively takes on the unique symptoms for each patient on the autism spectrum. Some treatment programs take place at a patient's home while others are conducted with a trained therapist or a specialist (Autism Speaks Inc. 2010). Successful treatment for ASD is dependent on early diagnosis and a treatment plan that is specific for the patient. No single treatment works well for everyone. Several factors are taken into consideration when developing a treatment plan such as; the patient's strengths and weaknesses, the severity of symptoms, subtype of autism, age of patient, access to health care services, and associated physical or psychiatric conditions (Ghaziuddin 2005). The list below presents the characteristics of a generic treatment plan for a patient with ASD.

Essential characteristics of effective interventions for children with autism spectrum disorder

1) Start intervention programs as early as possible.
2) Intensive treatment, 5 days a week for a minimum of 5 hours per day.
3) Use of repeated planned teaching opportunities that are structured over brief periods of time.
4) Sufficient individualized adult attention on a daily basis.
5) Inclusion of a family component, including parent training.
6) Mechanisms for ongoing assessment with corresponding adjustments in programming (Brentani, Paula et al. 2013).

With the help of a good treatment plan, a physician's treatment goal should be to: allow a patient to have functional spontaneous communication; have social instruction or interpersonal communication in various settings; be able to maintain new skills and generalize

them to a real-life context; and to employ a behavior management system that results in non-punitive techniques to improve behavioral challenges (Brentani, Paula et al. 2013).

Deficits in social skills are pervasive and one of the distinctive characteristics of ASD (American Psychiatric Association 1994). Social skills training is an integral component of treating patients with ASD and the majority of such training requires parental and family involvement (Brentani, Paula et al. 2013). Often social skills training programs are based in schools and focus on interpersonal communication. Normally developing children are integrated as peer-facilitators and help autistic children learn how to greet others, share toys, and engage in conversation (Ghaziuddin 2005). Behavioral programs first use methods like the applied behavior analysis (ABA) which develop a behavioral treatment plan and then launch into a series of intensive targeted behavioral reinforcement (Cooper, Heron et al. 2007).

As compared to the general population, people on the autism spectrum have higher levels of social loneliness and anxiety (Gillott, Furniss et al. 2001, Bellini 2004). Cognitive-behavioral therapy (CBT) has been effective at treating anxiety and daily living skills in clinical trials (Wood, Drahota et al. 2009, Reaven, Blakeley-Smith et al. 2012). In one clinical trial, 78% of 7-11 year olds were positive responders to CBT (Wood, Drahota et al.).

Chapter 2. Pakistan

This study was conducted in a country that is geographically, economically, and culturally very different from industrialized western nations. To best understand the study population and the study sample, this chapter provides a brief overview of Pakistan and goes into detail about Karachi, the study site.

2.1 Profile of Pakistan and Karachi

Pakistan proclaimed independence from Britain in 1947 and is located in South Asia. It borders Afghanistan and Iran on the East; China on the North; and India on the West (Figure 1). Pakistan's boundary lines occupy the easternmost part of the Tigris Euphrates river system and has been home to Indus Valley civilizations since antiquity, 2800 BC –1800 BC. Throughout time the Indus civilizations were invaded by many diverse groups of people such as; the Huns (Jayapalan 2001), Persians (Art. 2000), Arabs (Wink 2002), Turks, Afghans (Bartel 1999), Mongols and the Europeans. As a product of this history, today's Pakistani people are largely multicultural and multilingual.

Pakistan is the sixth most populous country in the world (Directorate of Intelligence 2010) and has the second largest Muslim population in the world. Pakistan is divided into five provinces: Pakhtoon Khuwan, formerly known as the North Western Frontier Province (NWFP); Gilgit Baltistan, home to the Himalayan mountains; Punjab, the agricultural province; Sindh, the study site is the southernmost metropolis of this province; and Balochistan, located in the southwest of Pakistan and is the largest and the most scarcely populated province of Pakistan. Geographically, Pakistan is separated into three regions; the mountainous terrain of the North,

the arid plateaus of the west, and the well irrigated fertile land of Punjab and Sindh. Islamabad (the capital), Lahore and Karachi are the most populous cities of Pakistan.

In Pakistan, over sixty languages are spoken but there are three official languages: Urdu, English, and Sindhi (Kachru, Kachru et al. 2008). Although, Urdu is the most commonly spoken language of Pakistan, English is the lingua franca of most government ministries and higher socioeconomic classes. Pakistani physicians are expected to be proficient in both Urdu and English but their medical education is conducted strictly in English.

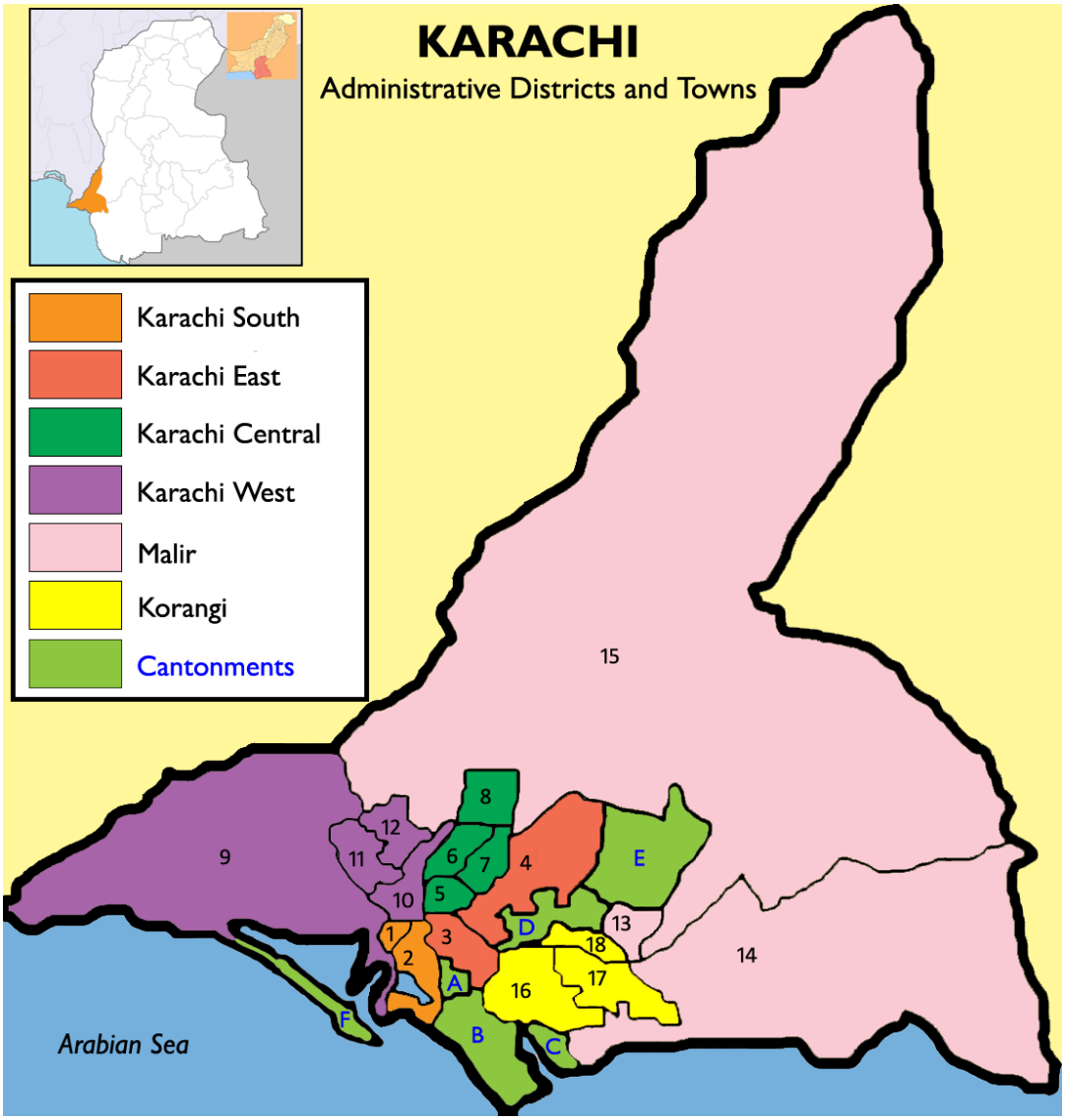
Since independence in 1947, Pakistan has sustained two major wars with neighboring India. This continued military tension results in heavy military expenditures for Pakistan (Directorate of Intelligence 2010). Three major factions have gained enough power to have influence on national policy; the military, civil services, and politicians. Power has shifted back and forth between military governments and democratically elected civilian governments. “As a result, many government policies have been made by and for the civil servants and politicians, who are either rich landlords or belong to the small coterie of rural or urban elites” (Ghaffar, Kazi et al. 2000). Due to the Pakistan’s expenditures on the military, healthcare expenditures remain low (0.8% of GDP) even compared to neighboring poorer countries such as Bangladesh (1.2% of GDP), Nepal (1.2% of GDP), and Sri Lanka (1.5% of GDP) (Ghaffar, Kazi et al. 2000).

Figure 1 Map of Pakistan (Central Intelligence Agency 2007)

Karachi is the southernmost metropolis of Pakistan and is located in the Sindh Province (Figure 2). It is amongst the top ten largest cities in the world by population. As a model of diversity, Karachi accommodates residents with a wide spectrum of socioeconomic status and various ethnic backgrounds. Rapid rural-to-urban migration has resulted in slums in Karachi, whose residents typically face much heavier burdens of disease (D'Souza and Bryant 1999). Karachi boasts the highest per capita income in South Asia. This bimodal distribution of wealth has resulted in an enormous economic disparity. Karachi's population size, economic, and

cultural diversity was the main justification for selecting it as an ideal study location for this observational study.

Figure 2 Map of Karachi (Wikimedia Commons contributors 8 May 2016)



DISTRICT SOUTH: 1. Lyari Town, 2. Saddar Town, DISTRICT EAST: 3. Jamshed Town, 4. Gulshan Town, DISTRICT CENTRAL: 5. Liaquatabad Town, 6. North Nazimabad Town, 7. Gulberg Town, 8. New Karachi Town, DISTRICT WEST: 9. Kemari Town, 10. SITE Town, 11. Baldia Town, 12. Orangi Town, DISTRICT MALIR: 13. Malir Town, 14. Bin Qasim Town, 15. Gadap Town. DISTRICT KORANGI: 16. Korangi Town, 17. Landhi Town, 18. Shah Faisal Town, CANTONMENTS: A. Karachi Cantonment, B. Clifton Cantonment, C. Korangi Creek Cantonment, D. Faisal Cantonment, E. Malir Cantonment, F. Manora Cantonment.

2.2 Health Sector in Pakistan

2.2.1 Politics and federal government responsibility

Before 1947, in pre-partition India the British Empire had established a strong health care system for government employees while on the other hand the health care system largely overlooked the civilian population (Mushtaq 2009). The British government built a few hospitals that still stand today; in 1860, Lahore Medical College was established and later named King Edward Hospital and Medical School (Mushtaq, 2009). Kind Edward Hospital's establishment launched a network of hospitals throughout the Indo-Pak sub-continent.

The federal government is responsible for establishing health care policies but the provincial governments are largely accountable for implementation of these policies (Ghaffar, Kazi et al. 2000). Due to scarce resources, the federal government provides a very basic health care framework, but it has proven difficult to coordinate these initiatives nationally. These difficulties have hampered large scale improvements in health care for the general public (Ghaffar, Kazi et al. 2000).

Health care provisions are divided into two parts; the public and private sector. The private sector is comprised of private hospitals and clinics spread throughout the rural and urban landscape. These services are typically provided based on a fee for service system. The private sectors serves nearly 70% of the Pakistani population (World Bank 1993). Neither the private nor the public sectors work under a regulatory framework and there is a lack of information regarding descriptive information about the Pakistani health care system. Consequently, there is little information relating to the financial resources involved in

maintaining the private sector or the public sector of the health care system (Ghaffar, Kazi et al. 2000). This makes it much more difficult to gauge where attention is needed to improve the system. “Healthcare problems are directly linked to the prevailing social, economic, and political systems that determine the allocation of resources in and outside the health sector” (Khowaja 2009).

The public sector is comprised of 10,000 facilities ranging from basic health care to tertiary referral centers (Ministry of Health 1995). Health care facilities in rural areas have three to four times the patient load of basic health care units in urban areas (Ministry of Health 1995). As of 1995, there were 22 tertiary care facilities in Pakistan but they are typically associated with academic institutions located in major cities (Ghaffar, Kazi et al. 2000).

2.2.2 Pakistan, an epidemiologic transition in the works

The theory of epidemiologic transition deals with large-scale changes in the demographic or sociological makeup of a region and their effect on disease occurrence and death. These complex patterns of disease and death correlate with how the demographic, social and economic makeup of a nation changes as it transgresses from a pre-industrial nation to an industrialized one. Nations that are in early stages of development tend to have high levels of fertility. During this transitions, “a long term shift occurs in mortality and disease patterns whereby pandemics of infection are gradually displaced by degenerative and man-made diseases as the chief form of morbidity and primary cause of death” (Omran 1971). Later in this transition, as pandemics recede, death rates for young children and women of reproductive age are reduced compared to other age groups (Omran 1971).

Pakistan has a young age structure with high fertility and low life expectancy; high maternal and child mortality in addition to high incidence of infectious and communicable disease (Afzal and Yusuf 2013). Understanding the stage of epidemiologic transition and the demographic makeup of a nation is important to epidemiologists and healthcare professionals because in developing countries healthcare professionals treat more patients with infectious disease while in industrialized countries physicians generally tend to patients with chronic disease. This balance is further complicated when working in countries that are in the midst of this epidemiologic transition (Afzal and Yusuf 2013).

In addition to being amidst a demographic transition, Pakistan has a bimodal distribution of wealth. This has resulted in two very different health care systems working in parallel: a private health care system for the higher socioeconomic classes; and a public and clinic-based healthcare system for the lower socioeconomic classes. In low and middle-income countries, quality in both public and private provider groups have proven to perform poorly but comparatively the private sector has better drug availability and performs better in some aspects of clinical care (Berendes, Heywood et al. 2011).

The epidemiologic transition of a country is directly related to a physician's medical awareness. In a developing country, physicians may be less aware of neurodevelopmental disorders such as Autism because the healthcare community is lagging behind in efforts to curb diseases that are immediately fatal and are focusing on infectious disease. Additionally, the large majority of patients are getting healthcare with a fee for service and may not be able to afford healthcare for children for social and communication disorders such as ASD.

Chapter 3. Research Design and Methods

3.1 Study Location and Population

3.1.1 Description of Study Population

The study sample for this project compromised of 348 general practitioners practicing in Karachi, Pakistan. Practicing physicians in Pakistan are required to be licensed and registered with the Pakistan Medical and Dental Council (PMDC). The year this study was conducted 116,009 were registered as practicing physicians in Pakistan; out of this number, 49,009 were registered in Sindh province and Karachi is the biggest city in Sindh (Khan 2004).

To establish a sampling frame, it was important to find a trusted database of registered physicians in Pakistan. The PMDC database is the most comprehensive and up to date record of clinicians in Pakistan but it wasn't available for our research purposes. Aga Khan University (AKU) has a small database of physicians who had attended Continuing Medical Education (CME) seminars at AKU. This registry was incomplete and would have led us to a misrepresentation of general practitioners (GPs) in Karachi; physicians who attend CMEs may be different from physicians who are not in AKU's database. Another source of data on practicing clinicians could be found within pharmaceutical companies' records. These pharmaceutical databases are used for marketing pharmaceutical products to all physicians and are regularly updated with new and existing records. We acquired the latest version of this database (Medi Publications: House of Medical Publications 2006) for establishing our sample frame and our sample population. This database of physicians listed 5,849 practicing physicians in Karachi.

3.1.2 Establishing Partnerships with Local Organizations

In the early stages of study planning and development, we established a working relationship with Aga Khan University in Karachi Pakistan. Aga Khan University is a prominent clinical research institution in Pakistan and has consistently received the highest rankings by the Higher Education Commission of Pakistan (Higher Education Commission 2012). Within the medical college at AKU we collaborated with the department of psychiatry and they were eager to provide support. Dr. Ehsan Ullah Syed, a faculty member in the department of psychiatry, agreed to be a local supervisor. He helped with establishing a research network and provided assistance with hiring an on-site research team.

Establishing a relationship with AKU helped us with developing credibility within the medical community and a rapport with hospitals, pharmaceutical organizations, and study subjects. We posted ads on the university noticeboards to hire a team of medical students who would help with conducting the study. These medical students were from Aga Khan University Medical College and Dow Medical College. They were instrumental in interviewing physicians for this study and for finding clinics around the city. The study team had local know-how about cultural practices and were knowledgeable about local transit, so we could get around the metropolitan city.

Dr. Hossein Rahbar was the off-site principal investigator on this project. I was the project coordinator and co-investigator on this project. My responsibilities included helping design the study, designing the questionnaire, getting research funding, managing study staff, training, conducting physician interviews, study logistics, data cleaning, data entry, and analysis.

I was also required to make presentations to AKU physicians about preliminary findings at the end of my time there.

3.1.3 Procedure for Establishing a Sampling Frame

We acquired official maps from the Karachi municipal headquarters. These maps did not provide enough detail to identify inner-city streets where many of the neighborhood clinics and smaller hospitals were located. In fact, some parts of the map were uncharted. Neighborhood residents often assigned names to smaller streets. Enrolling a representative sample was going to require going deeper into neighborhoods where we could find smaller clinics. Most physicians' clinics didn't use street address to help patients locate their clinics. Instead, physicians used common landmarks to identify their location or were already well known around a neighborhood that they didn't need to list a specific address. To find these clinics, we needed help from Karachi's residents and people who were very familiar with commonly used shops, relatively prominent street corners, and other cultural landmarks.

Our research team was based in Aga Khan University, which is located centrally in Karachi. To establish a representative sample of general practitioners in Karachi we needed to cluster sample recruitment from all of Karachi's twenty towns. Due to having limited resources such as; restricted transportation, cost of rental cars, personnel, and logistical constraints we drew a thirty-minute driving radius around Aga Khan University (AKU) and started recruitment within this radius. Two other considerations were taken into account when establishing this travel radius: the safety of the interviewers and enough geographic range for us to enroll enough subjects without oversampling from the same towns. Mid-study, we expanded the subject recruitment radius to encompass all twenty towns of Karachi. By this time, the study team felt

more comfortable getting themselves around the city and had become more familiar with how to locate inner-city clinics using local landmarks.

3.1.4 Study Sample

By utilizing a local research network, a study team that was familiar with the geographical layout of Karachi, and a database of practicing physicians, we were able to establish a sampling frame. The source database had names, clinic addresses, and phone numbers of physicians categorized by neighborhoods and towns. From our established study frame, subjects were drawn from each town of Karachi, as long as they had a listed address or general clinic location. In addition to clinics, general practitioners were also recruited from both government and private hospitals. This systematic convenience sample ensured that we encompassed the diverse demographic and geographic regions of the city of Karachi and there was representation from rural, urban, large hospital, and smaller clinic settings.

To prioritize study team organization and to streamline subject enrollment, each morning, we had a team meeting and identified which town we were going to focus on that day. After this, using our database of physicians working in Karachi, we identified which neighborhood within the respective town we were going to recruit subjects from. Every other physician was identified as a potential subject, but we went back to the top of the list if there weren't enough subjects in a neighborhood. During this study team meeting, each team member identified physicians' names with complete addresses from the database. A team member was sent to a study interview only if they were able to clearly understand a location from the database. Many of the addresses in this database had ambiguous addresses because most inner-city streets did not have names. The database used city landmarks to identify clinic locations. After a list of

potential subjects was identified, the study team went out in the field to conduct physician interviews. The physicians did not have any preconceived notions that they were going to be interviewed on a respective day nor were any public announcements made about this study being conducted. In addition to the team meeting, twice a week the study team met with me to review interview data, turn in paper forms for data entry into an electronic medical record system, and to work through any difficulties obtaining physician interviews.

3.1.5 Sample Size

To calculate the sample size for this project we needed to estimate how many GPs in Karachi would be aware of ASD. This sample, within a 5% margin of error and 95% confidence needed to be able to estimate the proportion GPs in Karachi who are knowledgeable of Autism. Taking for granted the established margin of error and the confidence interval, we also need the population standard deviation to estimate a sample size. We did not know the actual percentage of physicians were aware of ASD in Karachi nor were there any previous studies to help with this estimate. For this reason, we chose the largest estimate of standard deviation with a population proportion of 50%.

This calculation resulted in a sample size estimation of n = 384 GPs. The actual number of interviewed GPs was n = 348. In our post-hoc power analysis, the actual sample size was sufficient in detecting significant observed odds ratios with a power of at least 80%.

3.2 IRB and Database development

3.2.1 Institutional Review Board

The study questionnaire and study protocol were granted an expedited review by the Michigan State University Institutional Review Board (MSUIRB). Expedited status is granted to study proposals that pose no more than minimal risk to human subjects. Upon approval of the study proposal by the MSUIRB, I submitted the proposal to the Aga Khan University Institutional Review Board (AKUIRB). The AKUIRB meets to review research proposals on a monthly basis and this project needed to be approved before I arrived on site. The AKUIRB approved this study upon their first review.

3.2.2 Database development

After the study was approved by both the MSUIRB and the AKUIRB, I developed a web-based electronic data capture system to be able to enter study data from Pakistan. The Michigan State University Biomedical Research and Informatics Core (BRIC) provided server space and access to a proprietary electronic data capture system called RIX. Within this system, I developed an electronic version of the study questionnaire.

Data entry into a web-based data capture system provided several benefits. I was traveling back to the United States after collecting all the data and I did not want to rely on the transit of paper forms within the airline luggage system. These data were entered into RIX and sent to the BRIC servers from Pakistan. At this stage, the paper forms served as backups or our electronic data. Secondly, electronic data capture allowed me to improve data integrity and data quality. The RIX system allowed minimum and maximum values for string fields. Such

features prevented typographical errors during the data entry phase. Lastly, upon the completion of the data entry phase, the RIX system allowed me to directly extract these data to SAS for further cleaning and analysis.

3.3 Questionnaire Delivery

Survey design is considered the cornerstone of epidemiologic research and the "goal is to turn the process of everyday conversation into one of rigorous measurement, and the questionnaire is our protocol for that conversation" (CDC 2003). Pakistan is a British Commonwealth country and medical training is conducted in English. Physicians in Pakistan are expected to speak English. In developing the survey instrument for this study, it was important that questionnaire language was culturally congruent and used appropriate language with the study population in mind. There are differences between the English spoken in the US and the English spoken in Pakistan. The questionnaire was pilot-tested with two physicians who received their medical training in Pakistan but were working in the United States. Our pilot testers were able to advise on diction and on improving the delivery of the questionnaire.

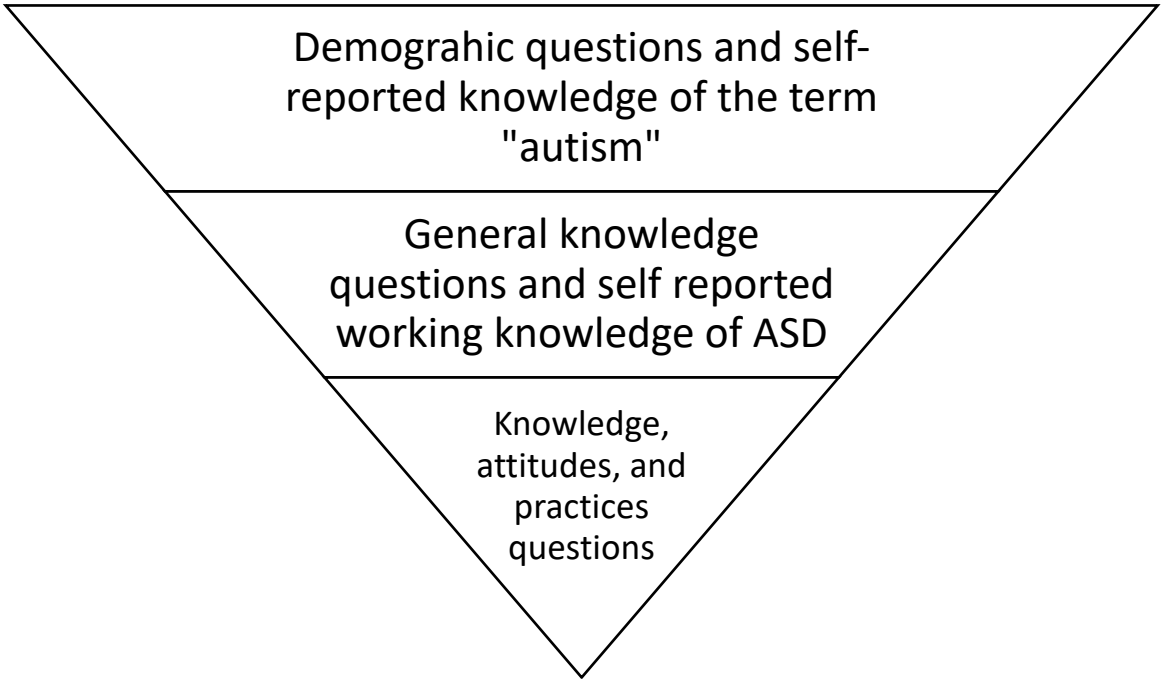
Secondly, it was also important that the surveying procedure was reproducible and ensured maximum validity. To make certain that we were recording valid responses from each physician, we implemented the questionnaire in-person and recorded the responses on paper. The questions were delivered identically to each subject. The questionnaire and the interviewer prompts were defined explicitly on a paper form. The interviewers had designated prompts for clarification of questions. Having a specified questionnaire facilitated the interview process. Since we were conducting a knowledge, attitudes, and practices survey, an in-person questionnaire also ensured that the subject didn't skip ahead in the interview. Some

downstream questions were only administered based on how physicians answered knowledge related questions. Lastly, administering the questionnaire in one language was likely to improve inter-rater reliability.

3.4 Questionnaire Design and Flow

The study questionnaire had four main sections; demographic information about the general practitioner, knowledge about ASD, attitudes towards autism, and the physician's practices or diagnostic methodology. All study subjects were asked the demographic information and whether they had heard of the term "autism". Out of the full sample, only GPs who had heard of the term were asked to proceed with questions regarding sources of exposure to the term "autism." We also asked this subsample of GPs some general knowledge questions about ASD. Next, the GPs were asked whether their understanding of ASD allowed them to make an appropriate diagnosis or referral, in other words, whether they had a working knowledge of ASD. Subjects who responded affirmatively completed the whole questionnaire including questions to access their knowledge and gauge their attitudes and practices about ASD. The Results section goes into further detail about this questionnaire flow but Figure 3 presents the general questionnaire flow for subjects in this study.

Figure 3 Questionnaire flow for GPs in this study



3.4.1 Demographics

The demographics section of the questionnaire was designed to better understand the GP's medical background and to paint a clearer picture about their current medical practice. Specifically, the demographic section had questions about: the general practitioner's choice of medical school, ward rotations during medical school, areas of interest in the field of medicine, daily clinical workload, whether they belonged to a medical panel and how the majority of their patients funded their medical care.

Questions selected for this section were concise and to the point; the physician's time commitment was a major consideration. For this section, the study team and I utilized various methods to accurately gauge a general practitioner's daily workload. We asked how many children they saw weekly, the average time they spend with each patient, hours they work daily

and finally the total number of patients they see on a daily basis. These questions were distributed throughout this section of the questionnaire and were used to quantify physician workload.

3.4.2 Exposure to Autism Spectrum Disorders

This section gauged the GPs exposure to ASD and ASD related topics. If GPs had been exposed to ASD, we further probed about their source of knowledge about ASD. We asked all physicians whether they had heard the term “autism”. To investigate the best mode of communication to disseminate medical information we asked where the physician had heard about "autism.

Next, we asked the physician whether they knew the prevalence rates of autism globally and in the United States to understand what their perception of the ASD’s burden of disease. We asked how many children they suspect to be autistic out of every hundred children they treat. We also inquired about any governments, pharmaceutical or academic institutions that may have contacted them regarding ASD. Lastly, we asked whether they had a “working knowledge” about autism. Only physicians who thought they knew enough about autism to diagnose on the spectrum proceeded with the questionnaire.

3.4.3 Knowledge

This section assesses the subject’s knowledge about ASD. Only subjects who had indicated that they have been exposed to ASD during their medical career were directed to this section. The interviewer guided the GPs through various statements regarding ASD and the general practitioners were asked to respond whether they agree or disagree. The GPs

responded on a five-point Likert scale from 1(strongly agree) to 5(strongly disagree). These statements were a combination of theories about ASD that are agreed upon in the scientific community and outdated or recently discarded theories regarding the causal pathway of autism. The interviewers were trained to ask each question in the same tone and at the same speed. We hope that these subtle practices kept questionnaire delivery as objective as possible. Statements that accurately represent ASD and ones that have been scientifically disabused were delivered in a similar manner.

Likert scales were the most ideal format for these questions because they are an easily understandable method for people being interviewed and they also facilitate statistical analysis for population studies. Secondly, as compared to dichotomous response options, Likert scales allowed physicians to respond on a spectrum without being forced to take a strong stance. We hope that this method helped us better gauge the degree of agreement each subject had regarding questionnaire prompts. Lastly, using Likert scale response options dramatically reduced how much time we spend with each physician and the coded responses saved us from having to conduct natural language processing rules on the final data.

3.4.4 Attitudes and Practices

This section mimics the structure of the knowledge section of the questionnaire. Questions in this section were directed towards the subject's personal views towards ASD based on their exposure and knowledge. We made statements regarding ASD and asked whether the GP agreed or disagreed on a Likert scale.

3.4.5 Open Ended Questions

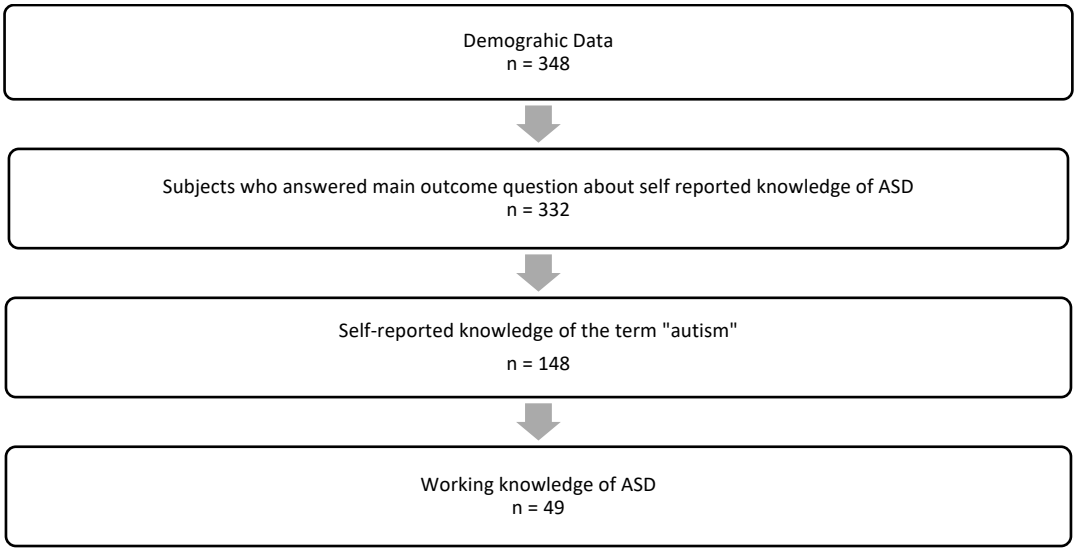
The questionnaire ended with two open-ended questions. The interviewees were informed that the questionnaire has ended and asked whether they would like to say anything in regard to ASD in Pakistan. The study staff that was administering the questionnaire then transcribed what the subject said.

In the early design stages of this study, we knew that little had been written about ASD in Karachi in medical journals nor in the lay media. An open-ended section was needed to capture data we might have missed in the structured questions. This question was also needed to be able to extract more information from the respondents regarding their feelings and understanding of ASD. The questionnaire was designed to allow comparative analysis amongst study subjects in regard to their knowledge, attitudes, and practices. This left a need for any free form responses the study subject wanted to give us for future studies.

Chapter 4. Results

This chapter covers the analysis of the study. The dataset was cleaned by Dr. Hossein Rahbar, the Principal investigator (PI) of the study and my advisor. I will start by asking demographic questions from the dataset to better understand the univariate distributions of GPs in our study. Next, I will explain patterns of these distributions using bi-variate correlations. After that, I will explore bivariate patterns that help evaluate the hypotheses. Then, I will build a logistic regression model to better understand risk factors for the outcome (knowledge of autism spectrum disorders). Lastly, to provide a more comprehensive picture of how ASD are diagnosed and treated in this population, I will do a subgroup analysis of general practitioners who said they are knowledgeable about ASD. This subgroup analysis will help us best evaluate the knowledge, attitudes, and practices of subjects who self-report to be knowledgeable about ASD. Figure 4 presents the general flow of this questionnaire. The subsequent sections in this study will present data collected for this study sample.

Figure 4 Flow of subjects through interview



4.1 Demographic Analysis

As detailed in the *Chapter 3: Research Design and Methods*, the study team recruited and interviewed GPs from Karachi. At the beginning of the study period, the GPs were recruited from a 30-minute driving radius around AKU and then this radius was expanded to encompass the all towns of Karachi. This provided a comprehensive and generalizable sample of general practitioners who were providing clinical care in the city of Karachi. These general practitioners had varying workloads and a diverse set of patients. Of the 332 subjects who answered the main outcome question about self reported knowledge about ASD, 224 (67%) of the subjects were men and 108 (33%) of subjects were women (Table 1). Nearly half of the subjects were older than 40 years (49%). At the time of the interview, the average age of the subjects was 41 years old, with the youngest practitioner being 25 years old and the oldest physician was 77 years old. Years since GPs graduated medical school has a bimodal distribution; the majority of the subjects (60%) either graduated within five years or more than 20 years ago. More

specifically, 83 subjects (25%) graduated within the last five years and 117 subjects (35%) graduated more than 20 years ago. The remaining subjects had graduated between five years and 20 years ago (40%). There was a similar distribution of years that the physicians had been practicing. More than half of the subject (53.6%), where born in Karachi and stayed local to establish their clinical care. The rest of the interviewed subjects were born elsewhere but moved to Karachi to practice medicine.

Table 1 Demographic Variables

Variable	Response	Frequency	Percent
Sex	Female	108	32.5
	Male	224	67.5
Age Group Frequency Missing = 13	< 30	78	24.4
	30 - 40	83	26.0
	≥ 40	158	49.5
Years since graduating medical school at the time of interview. Frequency Missing = 1	≤ 5 years	83	25.1
	5 - 10 years	56	16.9
	10 - 15 years	33	10.0
	15 - 20 years	42	12.7
	> 20 years	117	35.4
Years practicing medicine at the time of interview. Frequency Missing = 2	≤ 5 years	113	34.2
	5 - 10 years	49	14.9
	10 - 15 years	39	11.8
	15 - 20 years	30	9.09
	> 20 years	99	30.0
Birthplace	Karachi	178	53.6
	Other	154	46.4

Table 2 Mean age of GPs in the study sample

Age of General Practitioners at time of interview				
n	Mean	Std Dev	Minimum	Maximum
319	41.0783699	12.3849473	25	77

4.2 Clinical Care

We asked our GPs whether the majority of their subjects were coming from rural settings, urban settings, or if they had a mix of patients from urban and rural settings. Karachi is an urban metropolis but borders larger agricultural populations. Often, patients come to Karachi from these rural settings to get clinical care. The vast majority of the subjects' (80.3%) primary patient load was from urban settings but 19.7 % of GPs had patients from either a mix of rural and urban settings or from rural settings alone (Table 3). Next, we explored how patients were getting clinical care paid for. Pakistan does not have a socialized healthcare system and the majority of the Pakistan's clinical care is paid for out of pocket. When we asked GPs to identify the distribution of source of payment to the clinics and hospitals by patients, 79.9% of GPs reported that more than half of their patients were paying for clinical care themselves: 49 (12.2%) reporting 50%-75% and 208 (64.6%) reporting 75%-100% (Table 3).

Table 3 Variables describing the study subjects' clinical practice

Variable	Response	Frequency	Percent
Patients from rural vs urban settings. n = 325, Frequency Missing = 7	Rural	36	11.1
	Rural/Urban	28	8.6
	Urban	261	80.3
Distribution of a physicians' overall patient load that is personally funded. n = 322, Not specified = 10	0% - 25%	25	7.8
	25% - 50%	40	12.4
	50% - 75%	49	15.2
	75% - 100%	208	64.6
Distribution of a physicians' overall patient load insured by the private insurance. n = 217, Not specified = 115	0% - 25%	156	71.9
	25% - 50%	30	13.8
	50% - 75%	30	13.8
	75% - 100%	1	0.5
Distribution of a physicians' overall patient load insured by the military. n = 209, Not specified = 123	0% - 25%	203	97.1
	25% - 50%	2	1.0
	50% - 75%	4	1.9
	75% - 100%	0	0

4.3 Medical Education and Interests

A large majority of our subjects had graduated from government schools (93.6%), with the biggest proportion coming from Dow Medical College (31.6%). Only, 21 subjects (6.4%) had graduated from private medical schools (Table 4).

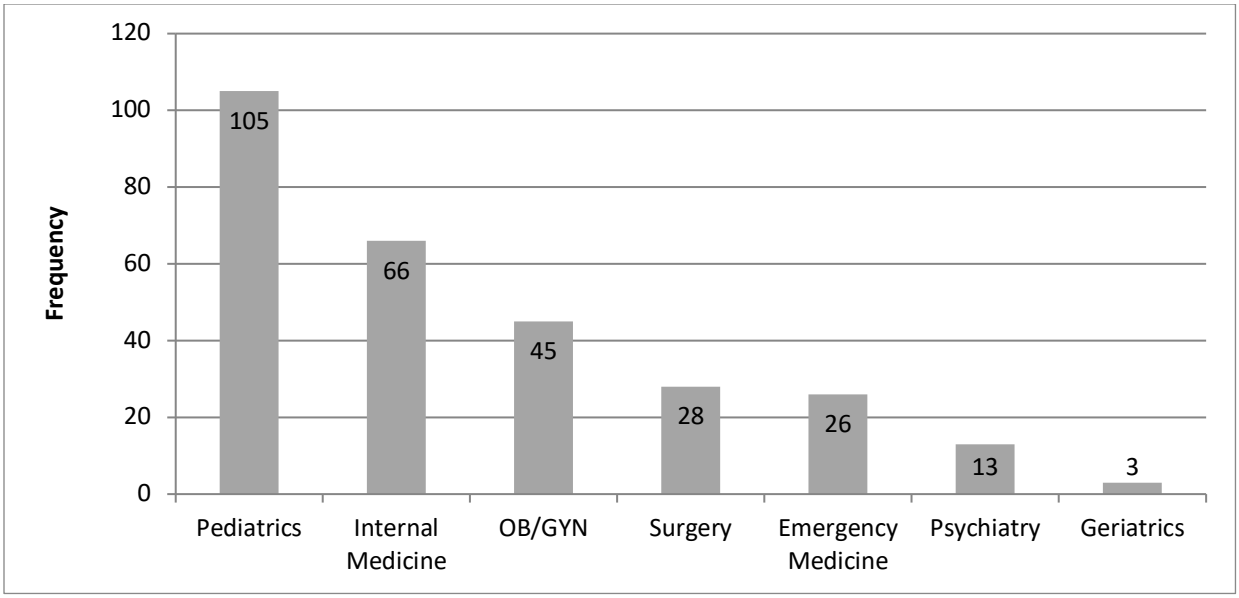
To better gauge a physician's personal interest in medicine we asked what area of clinical care they were most interested in. They were allowed to specify more than one field of personal interest amongst the following response options: surgery, OB/GYN, psychiatry, pediatrics, internal medicine, geriatrics, and emergency medicine. These questions gauge a physician's interest in medical topics outside of their educational curriculum (Table 4). More than a third (32%, n = 105) of the subjects, said they were interested in pediatrics. On the other end of the spectrum, only three subjects (<1%) were interested in geriatrics and 13 subjects (4%) were interested in psychiatry (Table 4).

Next, we asked GPs what ward rotations they had during their medical training. This question starts to investigate the subject's academic curriculum during medical school. During medical school, only 43 subjects (13.0%) had a ward rotation in psychiatry, while almost half (44.28%) of the subjects had a pediatric ward rotation. The most popular ward rotation was surgery (62.05%) while the least number of subjects (1.8%) were in a geriatric care ward rotation (Table 4).

Table 4 Variables describing GPs' medical education

Variable	Response	Frequency	Percent
Medical College Attended	Dow Medical College	105	31.63
	Sindh Medical College	85	25.6
	Liaquat Medical College	42	12.65
	Chandka Medical College	25	7.53
	Other	75	22.59
Government vs Private Medical school. Frequency Missing = 6	Government	305	93.56
	Private	21	6.44
Field of personal interest in medicine	Pediatrics	105	31.63
	Internal Medicine	66	19.88
	OB/GYN	45	13.55
	Surgery	28	8.43
	Emergency Medicine	26	7.83
	Psychiatry	13	3.92
	Geriatrics	3	0.90
Ward Rotation in Medical School	Surgical	206	62.05
	Internal Medicine	232	69.88
	Pediatrics	147	44.28
	OB/GYN	117	35.24
	Emergency Medicine	74	22.29
	Psychiatry	43	12.95
	Gerontology	6	1.81

Figure 1 Distribution of physicians' field of personal interest



4.4 Self-reported knowledge of the term “autism” and Logistic Regression

The first part of the questionnaire presented demographic data for the study sample and presented an overview of the study sample. This overview included the subjects educational background. The knowledge section of this questionnaire delved further into the GPs’ self-reported knowledge of the term “autism.” Of the sample of 332 subjects, 148 subjects had heard of the term “autism,” while 184 subjects (55.4%) had never heard of the term and 16 (4.8%) didn’t respond to this question (Table 5).

Table 5 Distribution of subjects who self-reported knowledge of the term "autism."

Self-reported knowledge of the term “autism”			
	Response	Frequency	Percent
Self-reported knowledge of the term "Autism" Missing = 16	Yes	148	44.6
	No	184	55.4

After getting a good understanding of the demographic makeup of the study subjects and calculating what percent of GPs who self-reported having knowledge of the term autism, I wanted to fit demographic variables to a logistic regression model. The dependent variable was self-reported knowledge of the term "autism" and I started with independent variables that included everything from the demographic section of the questionnaire. In a logistic regression model, records are included in the regression analysis if all variables in the final model have responses. Taking this into consideration, only 312 observations were used in this model.

Table 6 Logistic regression response profile

Response Profile		
Ordered Value	Self-reported Knowledge of ASD	Total Frequency
1	Yes	139
2	No	173
Total		312

The model's convergence was satisfied demonstrating that the model output could be used to predict an outcome. In this case, we could use our independent variables to predict if a physician is likely or unlikely to have heard of the term "autism." Below, the model fit statistics were used to develop the best model. After using forward, backward, and stepwise selection processes removed all non-significant variables were removed from the original model. At this point, certain variables were included back into the model because some variables, although not statistically significant, made clinical sense to be in the model. Variables included in the final model are described in more detail later in this section.

As variables were being added back in, I used both the model fit statistics to determine whether a good model was being developed. The model fit statistics include Akaike Information Criterion (AIC) and Schwarz Criterion (SC). AIC measures goodness of fit in a model but prevents

overfitting by penalizing the inclusion of too many independent variables in a model. The Schwarz Criterion is also used for model selection but penalizes the number of parameters in a model more strongly compared to AIC. In summary, the model fit statistics allow us to compare statistical models to each other and prevents underfitting or overfitting (Table 7).

Table 7 Logistic regression model fit statistics

Model Fit Statistics		
Criterion	Intercept Only	Intercept and 7 Covariates
AIC	430.811	406.393
SC	434.554	432.594
-2 Log L	428.811	392.393

Testing the global null hypothesis demonstrates that the independent variables in my model are able to provide a prediction for the outcome in the final model. The global null hypothesis of no effects of independent variables was rejected (Table 8).

Table 8 Testing global null hypothesis

Testing Global Null Hypothesis: BETA=0			
Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	36.4187	6	<.0001
Score	34.7213	6	<.0001
Wald	31.3396	6	<.0001

The resulting logistic regression model has the following variables: GP's age group; and whether they had ward rotations in psychiatry, pediatrics, or internal medicine. Using forward, backwards and stepwise selection, only two variables were statistically selected to be in the model: a ward rotation in pediatrics and a ward rotation in internal medicine. The GPs' age group, and whether they had ward rotation in psychiatry were later added back into the model because both of those variables are likely to inform their knowledge of ASD. The resulting, final

logistic regression model maintained its predictive ability and these latter variables were kept in the model (Table 9).

Table 9 Analysis of effects for logistic regression

Type 3 Analysis of Effects			
Effect	DF	Wald Chi-Square	Pr > ChiSq
Age Group	3	7.8911	0.0483
Pediatrics Ward Rotation	1	9.8076	0.0017
Psychiatry Ward Rotation	1	0.6414	0.4232
Internal Medicine Ward Rotation	1	8.1418	0.0043

The analysis of maximum likelihood estimates breaks down age group, the one categorical variable we have in our sample and examines statistically significant effect on the model (Table 10). The reference category was the age group of GPs who were older than 50 years. The self-reported knowledge of autism was higher amongst GPs ages 25-29 years relative to the reference group. The other two age groups, 30-39 years and 40-49 years did not have a statistically significant difference relative to the reference category. The same is true for GPs who had a ward rotation in pediatrics and internal medicine relative to those who did not (Table 10). As indicated in the Table 10, a positive coefficient indicates that the respective response presents an increased likelihood of self-reported knowledge about ASD.

Table 10 Analysis of maximum likelihood estimates

Analysis of Maximum Likelihood Estimates						
Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept		1	-0.2451	0.2213	1.2262	0.2681
Age Group	25-29 years^{+}	1	0.5719	0.2086	7.5171	0.0061
Age Group	30-39 years^{-}	1	-0.0407	0.2043	0.0398	0.8419
Age Group	40-49 years^{-}	1	-0.2693	0.2176	1.5322	0.2158
Pediatrics Ward Rotation	Yes^{+}	1	0.4283	0.1368	9.8076	0.0017
Psychiatry Ward Rotation	Yes^{+}	1	0.1661	0.2074	0.6414	0.4232
Internal Medicine Ward Rotation	Yes^{+}	1	0.4308	0.1510	8.1418	0.0043

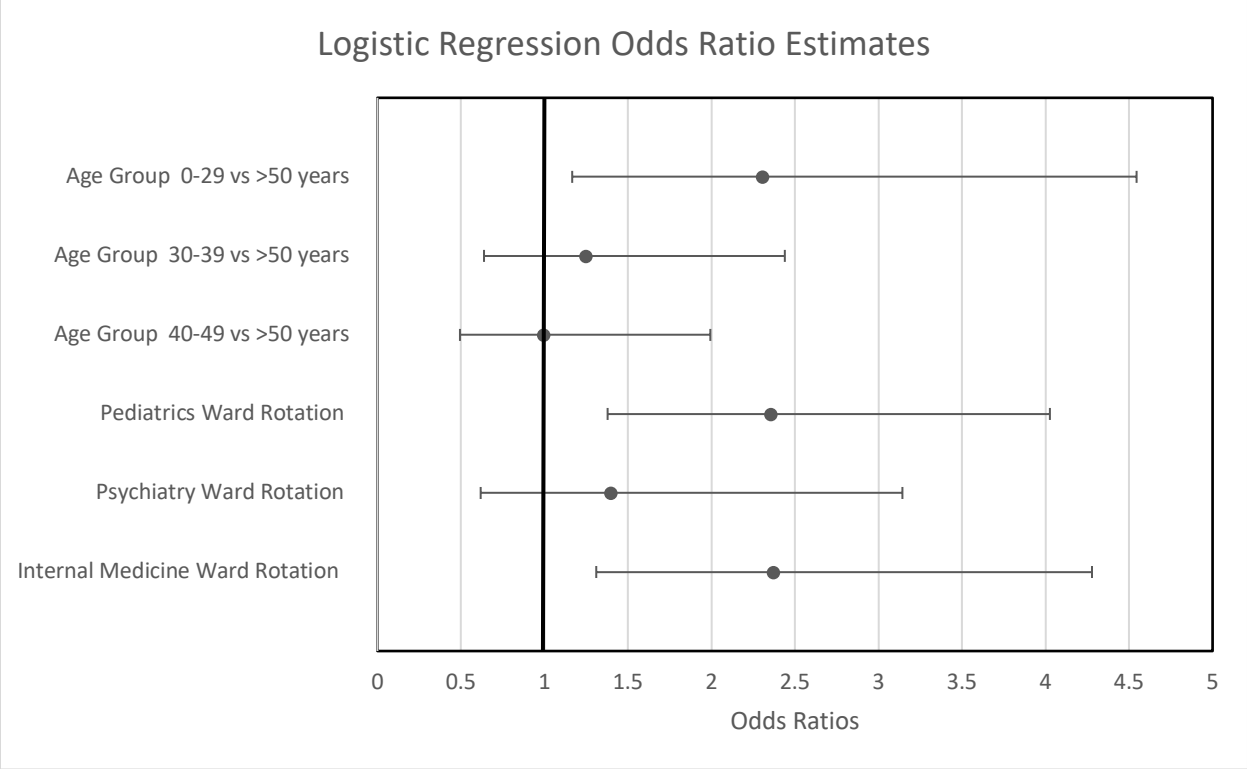
$^{-}$ Indicates that this response is the same or reduces likelihood for self-reported knowledge of ASD
$^{+}$ Indicates that this response increases likelihood for self-reported knowledge of ASD

Odds ratio estimates from a logistic regression model demonstrate how all the variables are contributing to the model. In this case, there is a significant difference in the model outcome when we compare physicians who are 25- 30 years old as compared to physicians who are older than 50. In other words, the youngest age group is predictive of self-reported knowledge of “autism” while GPs in the 30-39 and 40-49 categories did not differ significantly in their self-reported knowledge of the term “autism” from those who were older than 50 (Table 11). Similarly, a medical school ward rotation in pediatrics and internal medicine is predictive of a physician’s exposure to the term “autism.” In Figure 6, it is easier to see a graphical representation of how these odds ratio estimates are presented within this model. Notice that, point estimates for physicians who had ward rotations in pediatrics and internal medicine are greater than 1 and their 95% confidence intervals do not encompass 1.

Table 11 Odds Ratio estimates for variables in logistic regression model

Odds Ratio Estimates			
Effect	Point Estimate	95% Wald Confidence Limits	
Age Group 25-29 vs >50 years	2.302	1.166	4.545
Age Group 30-39 vs >50 years	1.247	0.638	2.439
Age Group 40-49 vs >50 years	0.993	0.494	1.993
Pediatrics Ward Rotation Yes vs No	2.355	1.378	4.026
Psychiatry Ward Rotation Yes vs No	1.394	0.618	3.143
Internal Medicine Ward Rotation Yes vs No	2.367	1.310	4.278

Figure 6 A forest plot of odds ratio estimates from the logistic regression model



In general, the association of predicted probabilities and observed responses shows how good this logistic regression model is at correctly predicting an outcome. In this case, we can see that the model has a much higher percent concordant than percent discordant. In other words, the model is able to predict an outcome accurately much more often than it predicts an outcome inaccurately. Similarly, the c-statistic, also known as the concordance statistic is

helpful in demonstrating the strength of a model. The c-statistic picks a randomly selected subject that has experienced an outcome (disease or condition) and gives the probability that their risk is higher than a subject who did not experience the same outcome. The c-statistic has to be greater than 0.5; if the c-statistic is close to 0.5, it is demonstrating that the resulting binary outcome variable, is akin to tossing a coin. For this logistic regression model, the c-statistic is 0.681; a high c-statistic indicates a better model (Table 12).

Table 12 Association of predicted probabilities and observed responses

Association of Predicted Probabilities and Observed Responses			
Percent Concordant	64.2	Somers' D	0.361
Percent Discordant	28.0	Gamma	0.392
Percent Tied	7.8	Tau-a	0.179
Pairs	24047	c	0.681

4.5 Knowledge

As described in Figure 4, only subjects who self-reported having knowledge about the term “autism” were asked about their source of knowledge about ASD. Then, they were asked subsequent questions to evaluate a deeper knowledge of ASD than just the term. This section presents their responses to questions regarding their source of exposure to the term “autism” and their knowledge about ASD.

4.6 Source of Knowledge about Autism

The most common source of self-reported knowledge of the term was from the general media. More than half of the study subjects (51.75%, n = 74) heard of “autism” from the media (Table 13). In Pakistan, the term “media” encompasses, television, print media, radio, and the internet. Television (41.9%), print media (39.2%), and the internet (35.1%) were the more

common sources for exposing our subjects to the topic of ASD, while radio (6.8%) was less commonly used for disseminating information on this topic (Table 14).

After media, medical journals were the second most common (48.9%, n = 69) source of knowledge about the term “autism” (Table 13). Next, 67 (46.5%) subjects from our study sample had heard about the term “autism” in medical school (Table 13). I was also interested in understanding whether non-profit organizations were conducting ASD related seminars in Karachi. This questionnaire revealed that if there were seminars conducted by external organizations, the subject material was not being presented to our study sample. Only, 4.9% or 7 subjects reported hearing about “autism” from an external organization (Table 13).

Table 13 Sources of knowledge about the term "autism"

Source of knowledge about the term “autism”			
	Response	Frequency	Percent
Media Frequency Missing = 5	Yes	74	51.8
	No	69	48.3
Medical Journal Frequency Missing = 7	Yes	69	48.9
	No	72	51.1
Medical School Frequency Missing = 4	Yes	67	46.5
	No	77	53.5
External Organization Frequency Missing = 5	Yes	7	4.9
	No	136	95.1

Table 14 Media sources of knowledge about “autism”

Media sources of knowledge about the term “autism”		
	Frequency	Percent
Television	31	41.9
Print Media	29	39.2
Radio	5	6.8
Internet	26	35.1

When asked whether general practitioners had attended a symposium on autism, 19 subjects (13.5%) indicted that they had and 122 subjects (86.5%) said that they had not (Table

15). The subjects who responded affirmatively were asked about the sponsor of these symposia and 9 subjects indicated that they had attended a symposium on autism at a university. Six indicating that the university was Aga Khan University. Out of the four subjects who attended a symposium with a pharmaceutical company, one of them indicate that the symposium was sponsored by Novartis. Two subjects mentioned the National Institute of Child Health as being a government sponsor. One subject mentioned Ida Rieu Welfare Association as being a Non-Governmental Organization sponsor.

Table 15 Frequency of subjects who attended symposia about ASD

Frequency of subjects who attended symposia on ASD			
	Response	Frequency	Percent
Autism Symposium Frequency Missing = 5	Yes	19	13.5
	No	122	86.5
	Government Organization	3	15.8
	Pharm Company	4	21.1
	University	9	47.4
	NGO	2	10.5

After establishing, how many subjects had heard of the term “autism,” (n = 148) we asked whether they had a working knowledge of autism. From this sub-sample, 49 subjects (29.3%) reported having working knowledge of autism (Table 16) . The next set of general knowledge questions gauged a deeper understanding of autism (Table 17). First, we asked our study subjects whether they could provide the prevalence of autism in the United States; five subjects (3.5%) responded to this question with an average response of 2,504/100,000. Next, we asked GPs the same question in regard to the global prevalence; eight subjects (5.6%) responded and had a mean estimate of worldwide prevalence at 2,524/ 100,000. Lastly, in this series of questions, we directed the topic to the subject’s own practice and asked how many

patients in their practice seem to be on the autism spectrum. In response to this question, 91 subjects responded; within their respective practices on average 1.4/100 subjects showed signs of ASD which translates into 1,400/100,000.

Table 16 Self-reported working knowledge of ASD

Working Knowledge of Autism			
	Response	Frequency	Percent
Working Knowledge	Yes	49	29.3
	No	83	49.7

Table 17 General knowledge questions about ASD

General Knowledge Questions			
	Response	Frequency	Percent
Do you have an estimate of the prevalence of autism in the US?	Yes	5	3.5
	No	138	96.5
Mean response to estimated prevalence in United States	2,504 / 100,000	5	
What about the prevalence of autism in children Worldwide?	Yes	8	5.63
	No	134	94.37
Mean estimated prevalence in the World	2,524 / 100,000	8	
Out of every 100 patients you see, how many of them seem to be on the autism spectrum	1.4 (prevalence of 1,400/100,000)	91	

To further evaluate the subjects' knowledge, in this questionnaire we presented the subjects with several statements and asked them to respond on a Likert scale: Strongly Agree, Agree, Undecided, Disagree, and Strongly Disagree. Table 18 presents GPs' responses to these statements and outlines the percentage of subjects who answered correctly and incorrectly. In other words, if a statement was correct and the subject both agreed or strongly agreed with the statement, they are presented with a correct response in this table. If the statement was

incorrect and they disagreed or strongly disagreed, they are presented with the correct response in this table. If an individual was undecided thy were not included in these analyses. On average, 58.7% of the time subjects answered these responses correctly.

Table 18 GPs' responses to statements about ASD

GPs' responses to statements about ASD				
	Correct Response to this question	Response	Frequency	Percent
Autistic children show detachment from their parents.	Agree	Responded Correctly	30	65.2
		Responded Incorrect	16	34.8
Autism is more prevalent in higher socioeconomic classes	Disagree	Responded Correctly	22	55.0
		Responded Incorrect	18	45.0
Autism is more prevalent in higher educational classes.	Disagree	Responded Correctly	24	61.5
		Responded Incorrect	15	38.5
Autistic children are not affectionate	Agree	Responded Correctly	17	38.6
		Responded Incorrect	27	61.4
Autism is a precursor for schizophrenia	Disagree	Responded Correctly	21	58.3
		Responded Incorrect	15	41.7
It is hard to distinguish between autism and schizophrenia	Disagree	Responded Correctly	31	73.8
		Responded Incorrect	11	26.2
Autism in children is mostly attributed to neglect in early childhood parenting	Disagree	Responded Correctly	24	52.2
		Responded Incorrect	22	47.8
Children tend to psychologically mature and grow out of autism	Disagree	Responded Correctly	28	65.1
		Responded Incorrect	15	34.9
Total Average		Average Correct Responses		58.7
		Average Incorrect Responses		41.8

Table 19 Bivariate analysis of knowledge statements and whether the subject graduated before or after 1990

Bivariate analysis of knowledge statements and whether the subject graduated before or after 1990				
Knowledge Statement	Graduated after 1990	Graduated before 1990	OR (95% CI)	P Value
Autism is more prevalent in higher socioeconomic classes (n = 40)				
Correct response	17 (77.27)	5 (27.73)	8.84 (2.11,37.11)	0.002
Incorrect response	5(27.78)	13 (72.22)		
Autism is more prevalent in higher educational classes (n = 39)				
Correct response	17 (80.95)	7 (38.89)	6.68 (1.58, 28.29)	0.0076
Incorrect response	4 (19.05)	11 (61.11)		
Autistic children are not affectionate (n = 44)				
Correct response	10 (58.82)	7 (41.18)	0.71 (0.20, 2.50)	NS
Incorrect response	18 (66.67)	9 (33.33)		
Autism is a precursor for schizophrenia (n = 36)				
Correct response	14 (66.67)	7 (33.33)	1.75 (0.45, 6.82)	NS
Incorrect response	8 (53.33)	7 (46.67)		
It is hard to distinguish between autism and schizophrenia (n = 42)				
Correct response	19 (61.29)	12 (38.71)	1.9 (0.38, 9.70) *	NS
Incorrect response	5 (45.45)	6 (54.55)		
Autism in children is mostly attributed to neglect in early childhood parenting (n = 46)				
Correct response	15 (62.50)	9 (37.50)	1.39 (0.42, 4.51)	NS
Incorrect response	12 (54.55)	10 (45.45)		
Children tend to psychologically mature and grow out of autism (n = 43)				
Correct response	20 (71.43)	8 (28.57)	6.89 (1.68, 28.10)	0.0053
Incorrect response	4 (26.67)	11 (73.33)		
* Exact Confidence Limits				

In a bivariate analysis, we evaluated if there is a statistically significant correlations between whether a GP responded correctly to a statement and whether they had graduated before or after 1990 (Table 19). This bivariate analysis revealed three statistically significant correlations. Physicians who correctly disagree with the statement that autism is more prevalent in higher educational classes were more likely to have graduated after 1990 (Table 19). In reverse, physicians who graduated before 1990 were more likely to incorrectly think autism is common in higher socioeconomic classes. Similarly, GPs who incorrectly thought that ASD is more prevalent in highly educated families were also less likely to have graduated after 1990 (Table 19). Lastly, physicians had graduated medical school before 1990 also thought that children tend to grow out of autism (Table 19).

Figure 7 displays the data from Table 18 as a histogram. From this chart, you can see that the majority of the subjects responded correctly to 4 of the 8 statements. For additional bivariate analysis, GPs' response rates were organized into two categories: a high score and a low score. A high score was defined as five or greater accurate responses and a low score was defined as four or fewer accurate response. Then, in Table 20 these high and low scores to knowledge questions were compared to whether a GP graduated before or after 1990. These analyses revealed one statistically significant correlation. Physicians who were younger were more likely to score higher in their responses to these statements (OR (95% CI) 4.28 (1.00,21.37), p-Value 0.02). Even though the lower 95^{th} percentile of this calculations reaches 1, this variable demonstrates a strong correlation (Table 20).

Figure 7 Frequency of correct responses to knowledge statements about ASD

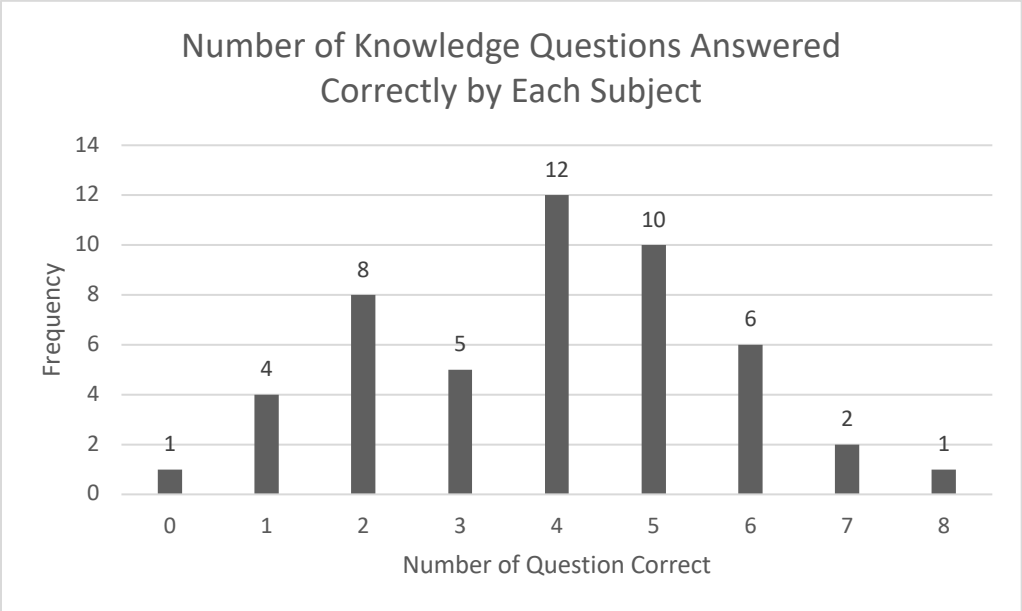


Table 20 Bivariate analysis comparing low knowledge scores and high knowledge scores with demographic variables

Bivariate analysis comparing low knowledge scores and high knowledge scores vs demographic variables				
Variable	High Knowledge score (5-8 correct)	Low Knowledge score (0-4 correct)	OR (95% CL)	P Value
Sex				
Male	11 (31.43)	24 (68.57)	0.34 (0.10,1.23)	0.07
Female	8 (57.14)	6 (42.86)		
Medical School graduation Year *				
After 1990	15 (51.72)	14 (48.28)	4.28 (1.00,21.37)	0.02
Before 1990	4 (20.00)	16 (80.00)		
Demographic makeup of majority of patients				
Rural	2 (28.57)	5 (71.43)	0.60 (0.10, 3.47)	0.29
Urban	16 (40.00)	24 (60.00)		
Surgery Ward Rotation				
Yes	11 (35.48)	20 (64.52)	0.68 (0.21, 2.25)	0.2
No	8 (44.44)	10 (55.56)		
OB/GYN Ward Rotation				
Yes	9 (52.94)	8 (47.06)	2.47 (0.74, 8.31)	0.08
No	10 (31.25)	22 (68.75)		
Psychiatry Ward Rotation *				
Yes	4 (40.00)	6 (60.00)	1.07 (0.19, 5.40)	0.28
No	15 (38.46)	24 (61.54)		
Pediatrics Ward Rotation				
Yes	13 (40.63)	19 (59.38)	1.25 (0.37, 4.25)	0.23
No	6 (35.29)	11 (64.71)		
Internal Medicine Ward Rotation				
Yes	14 (38.89)	22 (61.11)	1.02 (0.28, 3.75)	0.26
No	5 (38.46)	8 (61.54)		
Emergency Medicine Ward Rotation				
Yes	6 (54.55)	5 (45.45)	2.31 (0.59, 9.02)	0.13
No	13 (34.21)	25 (65.79)		
Self-reported exposure to autism from medical school				
Yes	10 (41.67)	14 (58.33)	1.27 (0.40, 4.02)	0.21
No	9 (18.37)	16 (64.00)		
Self-reported exposure to autism from medical journal				
Yes	8 (28.57)	20 (71.43)	0.36 (0.11, 1.19)	0.06
No	11 (52.38)	10 (47.62)		
Self-reported exposure to autism from media (TV, Radio, Internet)				
Yes	10 (41.67)	14 (58.33)	1.19 (0.37, 3.79)	0.22
No	9 (37.50)	15 (62.50)		
* Exact Confidence Limits				

4.7 Attitudes and Clinical Practices

This last section of the questionnaire examines physician attitudes and practices towards their patients who are presenting with symptoms of ASD. Most physicians agreed that children on the autism spectrum should receive special education (80%, n = 48) and though that autism holds a social stigma in their respective communities (61.7%, 37) (Table 21). GPs in this study informed us that most parents in Pakistan did not think that their children were at risk of having ASD (70%, n = 42). When we asked whether GPs thought that diagnosing a child with autism would lead to discrimination against the child, we got mixed responses. From within this sub-sample, 29 subjects (48.3%) thought their ASD patients were likely to be discriminated against while 28 subjects (46.6%) thought their ASD patients would not face discrimination (Table 21).

Table 21 Statements evaluating GPs' attitudes towards ASD

Statements Evaluating GPs' Attitudes Towards Autism Spectrum Disorders			
	Response	Frequency	Percent
In your opinion should autistic children receive special education?	Strongly Agree	23	38.3
	Agree	25	41.7
	Undecided	2	3.3
	Disagree	6	10.0
	Strongly Disagree	4	6.7
Do you think autism holds a social stigma in this community?	Strongly Agree	13	21.7
	Agree	24	40.0
	Undecided	8	13.3
	Disagree	12	20.0
	Strongly Disagree	3	5.0
Do you believe that diagnosing a child with autism will lead to discrimination against this child?	Strongly Agree	6	10.0
	Agree	23	38.3
	Undecided	3	5.0
	Disagree	20	33.3
	Strongly Disagree	8	13.3
In general, there is a negative opinion towards children diagnosed with autism.	Strongly Agree	11	18.3
	Agree	33	55.0
	Undecided	4	6.7
	Disagree	10	16.7
	Strongly Disagree	2	3.33
Parents in Karachi Pakistan tend to think their children are at risk of autism.	Strongly Agree	0	0
	Agree	9	15.0
	Undecided	9	15.0
	Disagree	27	45.0
	Strongly Disagree	15	25.0

4.7.1 Open ended questions

At the end of the interview and after a series of questions regarding GP's attitudes and practices towards ASD, I included two open ended questions. The first question asked if the GPs had any general opinions about the prevalence of autism in Pakistan (Table 22). The last question asked GPs if they had any additional comments as we closed out the interview (Table 23).

In response to these questions, 68 subjects responded to the first and 16 left a comment for the last question. I read through all the responses and established that there are four categories that encompassed physicians' thoughts on ASD: increasing general community awareness campaigns in Pakistan (38, 56%), dealing with the social stigma of ASD (5, 7%), improving medical infrastructure to treat ASD (23, 34%), reducing vaccine administration because they may cause ASD (2, 3%), and reducing consanguineous marriages in Pakistan (4, 6%) Table 22.

Table 22 Open-ended response categories

Open ended response categories	
Open ended response category	Frequency of coded responses
Awareness about ASD	38 (56%)
Reducing the social stigma of ASD	5 (7%)
Improving medical infrastructure	23 (34%)
Not giving children vaccines	2 (3%)
Reducing consanguineous marriages	4 (6%)

Table 23 Selected quoted comments from GPs

Subject	Quoted comment text
2046	Autism is largely unreported. In psychiatric practice since (sic)10 years he has not seen a single autistic child. However, a few days ago parents brought a child to him for information. The doctor though the child was autistic based on behavioral symptoms
1009	note -considers this disease to be of affluent nations (Europe, USA) -believes that a disease such as autism does not exist in Pakistan because small nucleated families allow for plenty of interaction
2008	1. Has a grandson who is autistic and is receiving successful speech and behavioral therapy in U.K 2. Perhaps antibiotics and premature birth of grandson may have played a role in his becoming autistic 3. Other two siblings are normal (firborn (sic) was autistic
785	I am a physician, but I am barely getting by because of my wife's medical bills. I work 15 hrs/ day and so do many other GPs in Pakistan. We don't have time to go to CMEs [continuing medical education seminars]

Chapter 5. Discussion

ASD affect millions of people worldwide. Even though we do not understand the etiology of ASD, early intervention has proven to show improvement in social, communication, and behavioral outcomes. The global healthcare community has expressed increasing concern regarding the burden of disease due to ASD worldwide (Wing and Potter 2002, Barbaresi, Katusic et al. 2006). Before this study was conducted, epidemiologists in the United States and other developed countries around the world were establishing the prevalence of ASD to better understand the burden of disease from ASD (Fombonne 2002, Newschaffer, Falb et al. 2005). To better understand the burden of disease of ASD in Pakistan, first, we need to establish how knowledgeable Pakistani general practitioners are about ASD. Then, we must explore their attitudes and clinical practices around the diagnosis of ASD. Only after understanding if Pakistani GPs are able to diagnose or refer an autistic child properly could future research establish the burden of disease of ASD in Pakistan.

In regard to mental health, in South Asian countries GPs are the first line of clinical care in a public health setting (Chisholm, James et al. 2000). This is especially true in Pakistan because bigger hospitals are centralized, and the majority of clinical care is provided by neighborhood health practitioners (Uplekar, Pathania et al. 2001). For a large majority of clinical care needs, a patient can get outpatient treatment at a GP's office and return home to recover. For more intensive clinical care, patients are typically referred to a specialist or a hospital. This path to receiving healthcare is typical even when public services are available (Bennett, McPake et al. 1997). In an ideal scenario, a child on the autism spectrum is diagnosed early in their childhood and then referred to respective treatment programs to receive a

customized regimen of care (Al-Qabandi, Gorter et al. 2011). A combination of early diagnosis and treatment can yield an ideal outcome and improved quality of life for a patient with an ASD (Bennett, McPake et al. 1997). On the other hand, a child may end up spending the rest of their life not being able to function in society if they do not receive a diagnosis in time or are misdiagnosed. This is especially true when an early diagnosis results in access to services which may include early intervention (Al-Qabandi, Gorter et al. 2011).

In this study sample, the GPs' self-reported knowledge of the term "autism" was much lower than expected; a majority (n = 184, 55%) of the GPs had never heard of the term, and of the GPs that self-reported knowledge of "autism" (n = 148, 42%), only 29% (n = 49) reported that they had a working knowledge of ASD. A working knowledge of ASD indicated that the GP would be able to diagnose or refer an autistic patient to a specialist. These findings are especially alarming because at the time of these interviews, many countries around the world had widespread public health campaigns built around ASD, and ASD were a major conversation in the global health care community (Fombonne 2002). Physicians in the developed world were establishing and refining diagnostic criteria to properly treat patients with ASD (Newschaffer, Falb et al. 2005).

To better gauge Pakistani physicians' knowledge, attitudes, and practices in regard to ASD, we needed to evaluate how they are learning about ASD, how continuing medical education seminars are conducted, how pharmaceutical companies impact their medical education and lastly, what phases of clinical translation Pakistan is in when it comes to ASD research.

5.1 *Factors most likely to predict knowledge of the term "autism"*

For a primary care physician, even knowing the term "autism" can lead to a greater understanding of ASD or lead a GP to refer a patient to a specialist. As an initial approach to understanding physicians, a simple question about a GPs' knowledge of the term "autism" was incredibly informative about the knowledge transfer of medical information in this healthcare community. As addressed later in this chapter, a GPs' medical school education was highly predictive of their current knowledge about ASD. As I was modeling the outcome variable of knowing or not knowing the term "autism," a medical school ward rotation in internal medicine and pediatrics ward rotations were both predictive independent variables. Similarly, the youngest category of physician age groups, 25–29-year-old physicians, were more likely to know of the term.

These correlations demonstrate that in this population if a physician was taught about ASD in their medical school curriculum, they were most likely to take that knowledge with them to their respective clinical practice. Both pediatrics and internal medicine ward rotations are more likely to facilitate the topic of mental health, especially when compared to ward rotations in surgery or obstetrics and gynecology. There are two things to consider in regard to a GP's age being a predictive factor in their general knowledge of ASD: younger physicians might have better recall of a lesser-known topic in regard to medicine, or older physicians may not have been taught about ASD in their curriculum.

Surgery was the second most common ward rotation (206, 62.1%) after internal medicine (232, 69.9%). Our study GPs' medical school interests showcase their preference for surgery and primary care for adults. Their medical school curriculum lacked attention to specialized

care for elders, only 1.8% of physicians had a gerontology ward rotation (6, 1.8%) and psychological health with only 13.0% of physicians having a psychiatry ward rotation (43, 13.0%). Psychiatry is a crucial component of a patient's medical care. Having learned about psychiatry along with primary care in a medical school setting results in holistic medical care for a patient's needs.

In a pre-industrialized nation, the popularity of certain ward rotations informs us where there is a need for health care practitioners in the country. Even though this study sample is comprised of GPs, their interests were relatively homogeneous and skewed toward surgery, pediatrics, and internal medicine. Shifting medical education to encompassed marginalized populations namely patients with specialized psychiatric needs would result in much better public health outcomes.

5.2 Continuing Medical Education and Other Sources of Medical Knowledge

When evaluating the medical knowledge for GPs in our study population, there are two primary variables to consider: a GPs' willingness to keep updated with the latest medical research and modes of access to medical knowledge. From the sub-sample of GPs who had already heard of "autism," the biggest proportion—79 subjects (25% of the sub-sample)—were exposed to the topic from the media, and only 30 (10%) had read about ASD in a medical journal. If GPs are mainly being exposed to new studies via the media, but then have limited resources to gain a deeper understanding of a new medical topic, it is less likely that they will be able to keep up with the latest research. Healthcare information is communicated in two

ways: general information is relayed to lay people via the media, and in parallel, it is disseminated to healthcare professionals via medical journals and continuing medical education seminars (CMEs). In this case, even if a physician had heard about the term “autism,” there was a lack of resources for them to explore the topic further.

Medical journals have been moving in the direction of an open-access platform compared to the traditional subscription-based model. However, at the time of this study, the majority of clinical research published in open-access journals had lower impact factors (Björk and Solomon 2012). In industrialized nations, physicians have access to medical journals mainly because the subscription rates are established to accommodate comparatively affluent hospitals and university subscriptions. For example, this study was published in the Journal of Autism and Developmental Disorders; the annual subscription rate for that journal is $199. For a GP in a private practice in Pakistan, subscription rates for multiple medical journals inhibit access to up-to-date medical knowledge.

CMEs are another important source of information for GPs to gain knowledge about advances in clinical care and help them learn about new, more beneficial methods of patient care. The objective of CMEs is to discontinue the use of outdated methods of patient care that may cause harm to patients (Bloom 2005). In more developed healthcare systems, GPs are exposed to updated medical education topics through many sources, but CMEs tend to be more comprehensive reviews of specialized medical topics. For example, in the US, these seminars are part of a physician's medical practice and a method for them to stay up-to-date with the latest research. In Pakistan, such seminars are available; 19 (13% of sub-sample) of the physicians knowledgeable of the term “autism” had attended such a seminar, but these CMEs

are not mandatory, nor regulated (Vakani, Jafri et al. 2011). Only 9 of these subjects had attended a seminar that was sponsored by a university rather than an external organization; this tells us that there is a chance that CME topics have a bias toward industry motivations.

These findings demonstrate that the healthcare system in Pakistan cannot rely on GPs' medical school training alone; CMEs are imperative to provide the most current medical care for their patients. In this study, lack of access to CMEs and medical journals resulted in GPs practicing treatment solely based on their medical school curriculum, which places an emphasis on only four years of clinical training. Furthermore, medical school was decades ago for some GPs; recent graduates had more exposure to the term "autism" and were subsequently more likely to accurately answer deeper knowledge questions about ASD. In summary, this study found that physicians who graduated before 1990 scored lower on questions with a deep understanding of ASD than recently-graduated GPs. I will explore this finding further in a subsequent section.

5.3 Antiquated knowledge of ASD related topics

The knowledge, attitudes, and practices series of questions delved deeper into GPs' understanding of ASD beyond their self-reported knowledge. This investigation evaluates whether a physician would be able to make an accurate diagnosis and then be able to refer a patient to an appropriate specialist. To better understand the intricacies of how knowledge transfer takes place within a public health framework, we need to first understand clinical translation. Then we can explore a comparative analysis of other healthcare populations where a successful translation has taken place for ASD. This comparison helps establishes a frame of reference to understand where Pakistan is in their clinical translation of ASD.

5.4 Clinical Translation

Clinical translation is defined as the transfer of knowledge from the research bench to clinical practice (Waldman and Terzic 2010). Clinical practice often lags behind cutting edge clinical research. Even in industrialized nations, there is a heavy emphasis on reducing this lag between new discoveries and changes in clinical practice (Waldman and Terzic 2009). Clinical translation is delayed when there are barriers in communicating the most updated research with the clinical care community at large. These barriers are further amplified when the lay media is not making the general population aware of a new discovery.

As addressed in the background section, the US healthcare system went through its own clinical translation for ASD research in the 1950s and 1960s (Schopler 1978, DeMyer, Hingtgen et al. 1981). It took many years for the lay media to disabuse antiquated theories about ASD. Some would argue that the US is still in this transitional phase when it comes to best explaining ASD to the general public (Rai, Lewis et al. 2012). Learning from the transition of knowledge about ASD in the US, we applied some of the same antiquated ideologies to the questions we asked Pakistani GPs.

Physicians in this study sample showed a poor understanding of the epidemiology of ASD even when they had self-reported having a working knowledge of ASD. Follow-up questions for physicians who reported having a working knowledge of ASD were comprised of a series of statements. Some of these statements were correct and some were incorrect. These knowledge questions revealed that GPs had outdated knowledge about the intricacies of diagnosing and referring patients on the autism spectrum. There were 8 statements to test deeper knowledge about ASD; on average, subjects answered correctly 56% the time. From

within this sub-sample of GPs who reported having a working knowledge of ASD, almost half, 47% (15, n = 36), thought that autism was a precursor for schizophrenia, and 48% (22, n=46) of the subjects thought that autism is due to neglect in early childhood. Both of these statements about autism demonstrate that a noteworthy proportion of physicians are working based on outdated knowledge about ASD. A significant proportion of subjects, 40% (20), thought that autistic children tend to mature or grow out of autism; such a medical opinion could be obstructive to early diagnosis of ASD and prevent a patient from getting treatment.

To better understand the characteristics of GPs who were scoring lower on these knowledge questions, I developed a score to quantify how well physicians were doing and to evaluate other characteristics of physicians who were scoring low. Even though it was marginally significant in this case, physicians who graduated after 1990 were 4.2 times as likely to correctly answer 5 question out of 8 (95% CI [1.00, 21.37], p-value 0.02).

Lack of confidence about such a disorder leads to lack of diagnoses, misdiagnoses and a reduced number of appropriate referrals. If at the point of first contact with a healthcare professional, a child with ASD is turned away or misdiagnosed, it is less likely that they will get proper treatment throughout their lifetime. Even though the etiology for ASD is not well understood, there are many treatment options for children if they are diagnosed properly. This study demonstrates that a substantial size of the represented GPs are not adequately treating their patients who present with ASD.

5.5 Pharmaceutical Companies

As detailed in the methods chapter, in the planning stages of this study I needed an established database of GPs working in Pakistan. The most comprehensive database is

maintained by the Government of Pakistan and keeps records of the physicians who are registered. This database was not available to our study staff, but the second-best option was a database maintained by pharmaceutical companies in Karachi. From an early stage, it was obvious that pharmaceutical representatives were the primary source of education for a lot of physicians working in Karachi; while conducting our interviews, the waiting rooms were often crowded with pharmaceutical representatives. These pharmaceutical representatives are in GPs' offices to sell medications and provide updated pharmaceutical research. Often GPs' only contact with recent research is through these pharmaceutical representatives and if a pharmaceutical company is not investing in making drugs for a specific disease, the GPs are less likely to find out about it. In this study sample, only 4 subjects had attended a pharmaceutical sponsored-seminar about ASD.

5.6 Bimodal distribution of wealth and health

Pakistan is a pre-industrialized nation with a bimodal distribution of wealth. As we set out to conduct an observational study looking at how the general population of Pakistan is being treated, we learned that we were investigating two different healthcare systems: one serving the small, higher socioeconomic classes, and another healthcare system serving the much larger lower socioeconomic classes. Access to healthcare resources and care are very different when comparing the poorest quintile to the riches (Alam, Nishtar et al. 2010). Taking prenatal care as an example, women in the "richest quintile had a 35%, 38% and 20% higher probability of getting prenatal care, delivery by skilled provider and emergency obstetric care, respectively" (Alam, Nishtar et al. 2010).

When establishing a representative sample for this study, it was important to have representation from GPs serving the lower socioeconomic classes and GPs working at larger hospitals with a well-defined referral system. Our study sample was representative of large government hospitals, private hospitals, and private clinics. Physicians working in private hospitals have a well-established referral system, as well as more specialists who can treat referred patients. Not only is medical care for patients different amongst these two income brackets, but the opportunities for CMEs are very different. In other words, physicians who have access to bigger hospitals also have access to medical journals, lectures, specialists who are experts in a field, and a well-established referral system.

5.7 Findings from fieldwork

This study was the first project to investigate the Knowledge, Attitudes, and Practices (KAP) of ASD amongst health care workers in Pakistan. KAP studies are often the first in line of an observational research approach to better understand a problem dealing with the delivery of clinical care. The KAP study's theoretical framework contributes to the knowledgebase to better understand a sub-population, helps generates questions for future research and also establishes research methods for conducting observational studies in a new setting. As expected, this study generates more questions than it answers.

Conducting health survey research in Karachi posed several barriers and a successful execution to these barriers required that our team find creative timely solutions. I have listed these barriers and my solutions to conducting this study in all towns of the biggest metropolis in Pakistan.

5.7.1 Geographical Constraints

Locating physicians' offices in rural or inner-city urban city settings without the help of accurate maps or addresses was difficult. Often the doctors' offices in our database only had cultural and geographical landmarks to identify the location and these offices were usually found on unmarked roads. Such constraints often keep researchers from doing work within inner-city neighborhoods. I overcame this barrier by hiring study staff who were knowledgeable about different towns within Karachi. I also worked closely with a driver who was able to get access to city streets by talking fluently in several local languages.

5.7.2 Logistical barriers

When I arrived on-site, in Pakistan, I advertised this research opportunity at medical school campuses with a project description and a call for medical students to apply for research staff positions. Logistically, it was difficult to manage the availability of study staff to match our schedule for conducting subject interviews. After the study staff was hired, I conducted weekly staff meetings to coordinate staff and to tend to difficulties in data collection. These meetings were imperative in successfully being able to enroll subjects for this study.

5.7.3 Cultural congruence of instrument

Before I launched this study, I was aware that our questionnaire needed to have language that was culturally congruent with the study population. As described in the methods section, the instrument was pilot tested with Pakistani physicians. After launching this study, I learned that a successful study was also dependent on some less obvious cultural practices. For example, many female GPs only preferred speaking with and treating female patients. Two of

our study staff members were women and I made sure they were conducting the interviews with female physicians.

5.7.4 Incentive for physicians

GPs in our study sample were giving us precious time out of their day so we could administer these questionnaires. In exchange for their time, we needed to give them a token of appreciation and some incentive for them to work with us. The IRB alerted us that this incentive could not be coercive, in other words, the incentive could not be so expensive that a physician would be forced to work with us. In the end, we commission a leather bag designer to make custom leather bookmarks that said “Pakistan Autism Project” in gold foil. These bookmarks were wrapped and presented to our study subjects at the end of the interview. We also hoped that after we left the physician, they would use these bookmarks as a reminder to become more aware of ASD.

5.8 Attitudes and Practices

We have spent all of this time evaluating physicians’ knowledge and delving into their understanding of topics related to ASD, but a huge consideration in the execution of clinical care is a physician’s attitude or general perceptions of a specific disorder. In this case, even though many of our physicians believed that there needs to be special education for patients with ASD, there were split responses as to whether a child would be discriminated against if diagnosed an ASD. This could lead to physicians intentionally not referring a patient to a specialist out of fear of what could happen to the child in their respective communities. Physicians also alerted us that parents weren’t concerned that their child was on the autism

spectrum; in other words, most of the patients they were treating came in presenting other primary care needs. Lastly, as described in the background section, Pakistan is a pre-industrialized nation. After finishing an interview with one physician, he stated that if he is spending most of his day treating cholera, he is less concerned about non life-threatening disorders. These attitudes and practices are important factors when evaluating a healthcare system different than in the United States.

5.9 Human Subjects Review

IRB approvals were obtained from Michigan State University (MSU) and from the Ethics Board at Aga Khan University (AKU), and the University of Texas Health Science Center at Houston (UTHSC-H).

5.10 Limitations

As described in the methods section, the sample was not randomized. Even though, I went through due diligence in acquiring a representative sample it is possible that the bias was introduced when identifying physicians for this study. Secondly, this study was based on an interview that relied on self-reporting knowledge about a topic. There could be recall bias in regard to some of the independent variables in our model. Furthermore, it is difficult to evaluate truthfulness of physicians who responded to follow up questions in regard to their self-reported knowledge of the term “autism.”

Even though, study team members used written scripts to conduct this interview different members of the study team visited assigned parts of the city This may have caused inconsistency in delivery of the interview. Taking these issues into account, many of the

interviews were conducted by me and strict supervision was provided for each study member. We also had weekly study team meetings throughout the interviewing phase of the study.

APPENDIX

QUESTIONNAIRE:

1. Demographic Information

Q1.1) Year or birth: YYYY

Q1.2) Sex: M/F

Q1.3) Birthplace:

Q1.4) Place of Residence for Most of Childhood: City, Country

Q1.5) On average, how many children (aged 2-12 y) are treated in your practice on a weekly basis? NUM

Q1.6) Generally, from what setting do your patients come? Rural / urban

Q1.7) In the city of Karachi, in which town is this clinic / hospital:

Q1.8) What is the name and location of the medical school you attended?

Q1.9) What year did you graduate from medical school? YYYY

Q1.10) What was your ward rotation during medical school?

1. Surgical
2. OB/GYN
3. Psychiatry
4. Pediatrics
5. Internal medicine
6. Geriatrics
7. Emergency Medicine
8. Other _____

Q1.11) Did you receive any further training post medical school?

Q1.12) How long have you been practicing? (In Years)

Q1.13) What percentage of your patients have their medical care funded by the following sources

1. Military
    a. 0% - 25%
    b. 25% - 50%
    c. 51% - 75%

d. 76% - 100%

2. Private insurance
    a. 0% - 25%
    b. 25% - 50%
    c. 51% - 75%
    d. 76% - 100%
3. Personally funded
    a. 0% - 25%
    b. 25% - 50%
    c. 51% - 75%
    d. 76% - 100%
4. Government Sponsored
    a. 0% - 25%
    b. 25% - 50%
    c. 51% - 75%
    d. 76% - 100%
5. other: _____
    a. 0% - 25%
    b. 25% - 50%
    c. 51% - 75%
    d. 76% - 100%

Q1.14) Are you on the medical care panel of a specific company/organization?

IF YES

Approximately, how many of your patients are from this company/organization?

Q1.15) On a typical day, how many hours do you practice? HRS

Q1.16) Although in general practice, do you have a current field of personal interest in medicine?

1)) Surgical	4) Psychiatry	7) Geriatrics
2) General Practice	5) Pediatrics	8) Emergency Medicine
3) OB/GYN	6) Internal Medicine	9) Other

Q1.17) How many patients (children and adults) do you see on a typical day? NUM

Q1.18) On average, how much time do you spend with each patient? HRS

2. Knowledge & Exposure to information about ASD

2(a) Exposure to information about ASD

Q2.1)Have your heard of the term "Autism"?

IF YES

Q2a.2)At medical school, were you exposed to the topic of Autism or Autism Spectrum Disorders (ASD)? (Y/N)__

Q2a.3)Have you read about Autism in medical journals? (Y/N)__

Q2a.3)Have you been contacted by any national or international organizations regarding autism or ASD? (Y/N)__

If YES, which organization _____.

Q2a.3)Have you been exposed to autism or ASD via national or international media? (Y/N)__

If YES, which mode of communication

a. Television
b. Print Media
c. Radio
d. Internet
e. Other: Please specify _____

Q2a.4)Do you have an estimate of prevalence rates of autism in the US? (Y/N)__

If YES, what is that estimate? ___ / 100,000

Q2a.5)What about the prevalence of autism in children worldwide? (Y/N)__

If YES, what is that estimate? ___ / 100,000

Q2a.6)Out of every hundred children being treated by you, how many of them are suspected to have autism?

Q2a.7)Have you been exposed to autism at a symposium or seminar?

If YES, exactly who organized it:

a. Government organized_____
b. Pharmaceutical company_____
c. University_____
d. NGO_____
e. Other, please specify:_____

Q2a.8) Did this source (s) give you a working knowledge about autism?

If YES, Next section

If NO, END

IF NO

(PROBE: "Until the very recently there has been little research about autism. In fact, we still do not have a cure for autism. You are not alone if you have not heard of this disorder. "

DEFINE AUTISM: Autism is a disorder of brain function that appears early in life, generally after the age of two. Children with autism have problems with social interaction, communication, imagination and behavior. Autistic traits persist into adulthood, but vary in severity. Some adults with autism function well, earning college degrees and living independently. Others never develop the skills of daily living, and may be incorrectly diagnosed with a variety of psychiatric illnesses. The causes of autism are unknown.)

Q2a.1) Have you been exposed to a disorder that fits this description?
If YES, Next question
If NO, END

Q2a.2)At medical school, were you exposed to the topic of such a disorder (ASD)? (Y/N)__

Q2a.3)Have you read about Autism in medical journals? (Y/N)__

Q2a.4)Have you been contacted by any national or international organizations regarding autism or ASD? (Y/N)__
If YES, which organization _____.

Q2a.5)Have you been exposed to autism or ASD via national or international media? (Y/N)__
If YES, which mode of communication

f. Television
g. Print Media
h. Radio
i. Internet
j. Other: Please specify _____

Q2a.6)Do you have an estimate of prevalence rates of autism in the US? (Y/N)__
If YES, what is that estimate? ___ / 100,000

Q2a.7)What about the prevalence of autism in children worldwide? (Y/N)__
If YES, what is that estimate? ___ / 100,000

Q2a.8)Out of every hundred children being treated by you, how many of them are suspected to have autism?

Q2a.9)Have you been exposed to autism at a symposium or seminar?

If YES, exactly who organized it:

f. Government organized_____
g. Pharmaceutical company_____
h. University_____
i. NGO_____
j. Other, please specify:_____

Q2a.10) Did this source (s) give you a working knowledge about autism?

If YES, Next section
If NO, END

2 (b) Knowledge

Answer the following questions from 1 (strongly agree) to 5 (strongly disagree)

(1) ---------- (2) ----------(3) ---------- (4) ---------- (5)
Strongly Agree Agree Undecided Disagree Strongly Disagree

Q2b.1) Autistic children show detachment from their parents

Q2b.2) Autism is more prevalent in higher socioeconomic classes

Q2b.3) Autism is more prevalent in higher educational classes

Q2b.4) Autistic children are not affectionate

Q2b.5) Autism a precursor for schizophrenia

Q2b.6) It is hard to distinguish between autism and schizophrenia

Q2b.7) I have a high level of accuracy in diagnosing autism spectrum disorders

Q2b.8) Autism in children is mostly attributed to neglect in early childhood parenting.

Q2b.9) Children tend to psychologically mature and grow out of autism

3. Attitudes

Answer the following questions from 1 (strongly agree) to 7 (strongly disagree)

(1) ---------- (2) ----------(3) ---------- (4) ---------- (5)
Strongly Agree Agree Undecided Disagree Strongly Disagree

1) In your opinion should autistic children receive special education?

2) Do you think autism holds a social stigma in this community?

3) Do you believe that diagnosing a child with autism will lead to discrimination against this child?

4) In general, there is a negative opinion towards children diagnosed with autism.

5) Parents in Karachi Pakistan tend to think their children are at risk of autism.

6) Autism is preventable.

4. Practices

Q4.1) How do you diagnose Autism Spectrum Disorders?

a. Use ADI-R or ADOS
b. General evaluation
c. Parents are given a questionnaire to fill out and note observation
d. DSM IV criteria
e. Other, specify _____

Q4.2) Please list some early indicators of autism in a 2 year old child

Q4.3)In Pakistan, are there any early diagnosis questionnaires in place for parents of autistic children? (Y/N)___

Q4.4) In diagnosing children with autism are the following symptom *necessary*, *not necessary but helpful*, and *not helpful* in diagnosis

(1)----------(2)----------(3)
Necessary Helpful but not necessary Not Necessary

Impaired social interaction
Impaired communication
Hallucinations
Restricted and repetitive behavior
Lack of eye contact
Confirmed Schizophrenia

Hearing voices
Language Disturbances
Hypersensitivities to certain environment
Depression
Anxiety

Q4.5) What other diagnostic behaviors do you use in your assessments?

Q4.6) What in your opinion can be done in decrease the prevalence of autism in Pakistan?

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