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Efficacy of Telegenetics: A Diagnostic Yield Comparison Between In-Person and Telemedicine Pediatric Genetic Evaluations

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EFFICACY OF TELEGENETICS: A DIAGNOSTIC YIELD COMPARISON BETWEEN IN-PERSON AND TELEMEDICINE PEDIATRIC GENETIC EVALUATIONS

by

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ABSTRACT

The purpose of this study was to investigate the efficacy of telegenetic services for pediatric genetic evaluations conducted by telemedicine by comparing it to in-person pediatric genetic evaluations. Research into the utility of telegenetics would greatly serve to identify if this is a preferred alternative service delivery model to bridge the gap in accessibility and reach a greater catchment area of the population, especially to those living in underserved and rural locations. This study was a retrospective review of electronic medical records of pediatric patients seen at Greenwood Genetic Center (GGC) for initial in-person genetic visits prior to the COVID-19 pandemic and initial telemedicine genetic visits during the COVID-19 pandemic. Primary indications were reviewed in conjunction with the final clinical assessment made by the geneticist at the time of visit. Diagnostic information from the clinical assessment was used to determine if a clinical diagnosis could be made, which was categorized into clinical genetic diagnosis (met clinical criteria with/without the need for molecular confirmation), environmental etiology, isolated anomaly, multifactorial etiology, within normal variation, and testing not indicated. If testing was indicated, results were categorized into diagnosed, undiagnosed, uncertain, or not completed. Both clinical assessment and genetic testing outcomes were used in the diagnostic yield comparison. We found that visit type did not have a significant effect on the likelihood of diagnosis. Identifying the similarities in diagnostic outcomes for patients seen by telemedicine may strengthen the

support for telegenetic services, improve accessibility to genetic services, and benefit both providers and patients.

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LIST OF ABBREVIATIONS

AAP..... American Academy of Pediatrics

ACMG..... American College of Medical Genetics and Genomics

ASD..... Autism Spectrum Disorder

CMA ..... Chromosomal Microarray

CMS .....Centers for Medicare and Medicaid Services

CPT ..... Current Procedural Terminology

DD.....Developmental Delay

EMR.....Electronic Medical Record

GGC ..... Greenwood Genetic Center

hEDS ..... Hypermobile Ehlers-Danlos Syndrome

HHS..... Human and Health Services

ICD9..... International Classification of Disease, Ninth Revision (up until 1999)

ICD10.....International Classification of Disease, Tenth Revision (1999 - Current)

ID .....Intellectual Disability

IP..... In-Person

IQ .....Intellectual Quotient

LP..... Likely Pathogenic

MCA .....Multiple Congenital Anomalies

MS-MLPA..... Methylation-Specific Multiplex Ligation-Dependent Probe Amplification

NGS.....Next Generation Sequencing

Path .....Pathogenic

PHE.....Public Health Emergency

TH .....Telehealth

VUS..... Variant of Uncertain Significance

WES ..... Whole Exome Sequencing

CHAPTER 1

INTRODUCTION

1.1 Current Genetic Testing Protocols and Diagnostic Yield in Pediatric Patients

Pediatric genetic evaluations aim to provide a specific diagnosis for noted signs and symptoms and these evaluations often include physical exam, history, and genetic testing. Although there are various referral indications for patients seen for a pediatric genetic evaluation, the most common indications include developmental delay (DD), intellectual disability (ID), autism spectrum disorder (ASD), and multiple congenital anomalies (MCA); the current standard of practice for individuals with these indications is chromosomal microarray (CMA) as a first-line test (Manning et al., 2010; South et al., 2013). CMA is further recommended as a first-tier test for individuals with features not specific to a well-delineated genetic syndrome. The current literature suggests CMA has a diagnostic yield for individuals with unexplained DD/ID, ASD, or MCAs of around 15-20%; this is higher than the ~3% diagnostic yield from karyotype, which is more likely to identify recognizable chromosomal syndromes (Miller et al., 2010). The current guidelines suggest a more targeted testing strategy is recommended for individuals who have a specific phenotype suggestive of a known genetic condition. For these patients, a more targeted gene sequencing panel may be a more cost-effective method in establishing a genetic diagnosis (Kiely et al., 2016; Retterer et al., 2016; Vissers et al., 2017).

Since the American College of Medical Genetics and Genomics (ACMG) published the practice guidelines for the use of CMA as a first-tier test, technology has

greatly improved and whole exome sequencing (WES) has enabled additional diagnoses in patients not diagnosed by CMA or other testing methods (South et al., 2013). Beginning in 2011, literature has suggested that WES should be considered as a first-tier test for certain indications due to a potentially higher yield than CMA, with a diagnostic yield of at least 25% (Clark et al., 2018; Retterer et al., 2016; Vissers et al., 2017). Guidelines currently do not exist for the use of WES as a first-tier test, largely due to the need for more research on the impact of results on clinical management in order to establish clinical utility and develop standardized guidelines (Malinowski et al., 2020). Since there have been few changes to the guidelines, CMA remains the recommendation for first-line testing for individuals with non-specific DD/ID, ASD, and MCAs. Due to an overwhelming amount of literature suggesting the value of WES in determining a genetic etiology, WES is generally considered a good option as a second-tier test for those who do not receive a diagnosis after first-line testing.

With a number of professional societies recognizing the importance of genetic testing in the etiologic workup for children with DD/ID and ASD, guidelines published by the American Academy of Pediatrics (AAP), the American Academy of Neurology, and the ACMG all recommend CMA and Fragile X testing as first-tier diagnostic tests for children with unexplained DD/ID with or without ASD (Filipek et al., 2000; Miller et al., 2010; Moeschler et al., 2014; South et al., 2013). It is suggested that more targeted testing or karyotype may be indicated following a physical exam, if family history is suggestive of a specific diagnosis, or if initial testing fails to establish a genetic diagnosis. With this approach, the identification of an underlying genetic cause may be found in up to 40% of patients (Kiely et al., 2016).

Vissers et al. (2017) reported data that suggest WES as a preferred first-tier diagnostic test in patients with complex neurological features in order to shorten time-to-diagnosis as well as reduce costs for unnecessary procedures, imaging studies, biopsies, etc. Although single gene testing and gene panels are commonly used when a specific disorder associated with a small number of genes is suspected, WES has become an advantageous testing strategy for patients with suspected disorders that are genetically heterogenous (Retterer et al., 2016). The clinical application of broader tests such as WES has been investigated to determine the utility in a broader range of clinical indications, outside neurodevelopmental disorders, DD/ID, ASD, and MCAs. In a recent study identifying the test yield based on primary indication, hearing, vision, skeletal muscle, and skeletal indications were some of the highest yielding diagnostic outcomes for WES (Retterer et al., 2016).

Due to the various referral indications for patients to be seen for a genetic evaluation, there may be clearer guidelines on testing strategy for some patients than there would be for other patients. This indicates that genetic providers may have different testing approaches based on indication. Additionally, the diagnostic yield of WES increases when trio testing (typically proband with both parents) is ordered versus testing ordered just on the proband (Miller et al., 2010; Retterer et al., 2016). Often, the price of testing increases with the inclusion of additional family members for genetic testing, so there may be variation between providers on the inclusion of family members if the cost or logistics to obtain samples are significant. The variation in testing strategy between providers may determine a different diagnostic yield, with various extrinsic factors such as insurance coverage and cost of testing playing a large role in the ability to order the

preferred test. Some insurance policies have their own established guidelines that can impact a provider's testing strategy and may limit testing options.

Despite the number of societies recognizing the importance of genetic testing in children with development disabilities, Kiely et al. (2016) sought to determine the rate at which these children undergo genetic testing. They found that less than one-third of individuals with ID, DD, and/or ASD have ever undergone genetic testing. Although this study did not assess the reasons why children did or did not undergo genetic testing, there were a number of factors proposed that may have contributed to their findings. One finding of interest to this project was that children who were reported to have seen all needed service providers within the year were more likely to have undergone testing than those who did not. This finding suggests a broader issue in access to healthcare and that difficulty obtaining genetic services may be contributing to the lower rate of testing in individuals with developmental disabilities who should be offered testing. Potential barriers such as lack of adequate transportation and access to care may also be contributing to the underutilization of genetic testing in this population (Kiely et al., 2016).

1.2 Disparity in access to genetic services

Access is an important concept in healthcare and has prompted innovation, technology, and the development of alternative services to minimize the inequality that can be seen across a variety of contributing factors. Access is most frequently considered the ability or willingness to enter the health system, and includes specific areas that contribute to the concept of access such as: availability, accessibility, accommodation, and affordability (Penchansky & Thomas, 1981). Availability involves the supply and

number of existing services, while accessibility is associated with the location and distance required to obtain services. Accommodation refers to the relationship between the organization of services offered as well as the perception of appropriate services provided, and affordability is referred to as the ability to pay for services (Penchansky & Thomas, 1981). Although we will not directly analyze costs or affordability (because data collected would falsely represent services due to the current policy changes under the 1135 waiver, which allows Medicare beneficiaries to receive a wide range of previously unavailable telehealth services), we hope to address and expose other areas addressed above in minimizing the disparities in access to genetic services.

Much of the disparity and inequity in services can be attributed to a shortage in genetics providers, with most practicing in cities serving large geographic areas, which in turn can require some patients to travel far distances for genetics services. Rural and underserved areas are frequently impacted as they are less likely to have adequate access to reliable public transit, may be impacted by longer wait times for outreach clinics, or be required to travel far distances for services. This can put a significant burden on both the provider and families seeking services. The inaccessibility of genetics services in a pediatric setting means that many children with genetic conditions will receive a delayed diagnosis or remain undiagnosed. This is concerning, as a genetic diagnosis may alter medical management and/or provide access to therapies that could benefit the patient and the family (Lea et al., 2005; Penon-Portmann et al., 2019).

Geographic distance between a patient population and the nearest genetics provider is an issue that is not limited to the United States and has been addressed in other countries through the expanded use of telegenetics services, which is the use of

telehealth in providing genetic services (Hopper et al., 2011; Otten et al., 2016; Pestoff et al., 2019). However, there are considerable issues in the United States with maldistribution of genetics professionals concentrated in large cities. Practice limitations and insurance restrictions are a state-by-state issue and can be particularly burdensome for larger states where significant portions of the population may be impacted by poverty or live in rural areas (Lea et al., 2005; Penon-Portmann et al., 2019).

A study in California reported a provider to patient ratio of 1:330,000 for medical geneticists and 1:100,000 for genetic counselors (Penon-Portmann et al., 2019). These numbers highlight the challenges regarding geographic distribution in relation to the genetics workforce shortage. For this particular study, analyzing zip code data revealed that the average distance patients were traveling to be seen by a genetics provider was 76.6 miles. The authors further determined the role insurance may have in how far a patient may need to travel, and identified that the median distance traveled for publicly insured individuals was greater than that of privately insured individuals (public= 69.3 miles; private= 45.2 miles), with 71.4% of people traveling from rural locations having public insurance (Penon-Portmann et al., 2019). This emphasizes the need to minimize the limitations that travel may impose on families seeking a genetics evaluation. Telegenetics may address some of the concerns with distance; half of genetics specialists providing telemedicine estimate their geographic reach to be greater than 200 miles (Terry et al., 2019).

Additionally, one of the proposed advantages of telegenetics is the effect it may have on long wait times for genetics evaluations (Kubendran et al., 2017). Long wait times can be anxiety-provoking for families seeking a diagnosis and may delay impactful

medical management changes that would come from receiving a diagnosis. The use of a collaborative service delivery model, including a pediatrician and genetic counselor, has been used as an approach to provide telegenetics services to underserved areas, while also decreasing the wait time for an appointment (Kubendran et al., 2017). Similarly, it was found in other research utilizing a delivery model including a pediatrician and genetic counselor, that over two years, the wait time for a genetics evaluation was reduced from 16.9 months to 3 months (Stalker et al., 2006). Receiving a timely diagnosis can have a substantial impact on a patient and family as a diagnosis may provide additional recommendations for services, screenings, and/or treatment.

As the field of genetics advances, so does the technology and ability to diagnose and treat patients with genetic conditions. With this in mind, equity of access and quality of services provided is imperative. More research is needed in determining the diagnostic outcome and evaluating best practice models in making alternative services as comparable as possible to that of an in-person evaluation.

1.3 What is telemedicine and what is its role in genetics?

Telemedicine can be defined as the use of electronic and communication technology in patient care for diagnosis, monitoring, and therapy (Pestoff et al., 2019; Vrečar et al., 2017). Over the past few decades, telemedicine was broadened to include telehealth, which is characterized by the geographic separation between patient and provider; however, both terms are used interchangeably (Wade et al., 2010). An increased interest in the use of telehealth has developed over the past 20 years across several medical specialties. Much of this interest arises from the need to make patient care more accessible, especially when there are a limited number of specialty providers or an

uneven geographic distribution of physicians. Addressing challenges in access to care will require innovative technologies and/or service delivery models to improve access to genetics services in remote or underserved areas.

Currently, there are four modalities that encompass ways of delivering telemedicine: store-and-forward, remote patient monitoring, mobile health (mHealth), and live video (Vrečar et al., 2017). Store-and-forward can be defined as the transmission of recorded health information to a practitioner, such as sending digital X-ray images to a radiologist. Remote patient monitoring technology is the collection of electronic information transmitted from a patient and sent to a provider in a different location. Mobile health (mHealth) incorporates the use of cell phones or tablets to provide healthcare and education. Live video (synchronous) technology uses audio and videoconferencing to provide interaction between the patient and provider (Vrečar et al., 2017).

Of the modalities described, the most commonly used by genetics professionals is live videoconferencing to provide real-time counseling or genetic evaluations, which is also referred to as telegenetics. Although store-and-forward and mHealth have been described in the literature as potentially useful for the field of genetics, live video conferencing is the one that has been suggested as a potentially viable alternative to an in-person genetic consultation (Vrečar et al., 2017).

As our knowledge of genetics and the role it plays in our understanding of disease continues to expand, so does the number of patients who require genetic services. This has profoundly influenced the increased interest in delivery of telehealth in genetics, or often referenced as telegenetics, as an additional option for patients. While this is easier

for providers who are not performing a physical exam, such as in cancer or prenatal genetics, telegenetics is an area that needs further exploration in pediatric and general genetics clinics. A recent study highlighted the need for a better understanding of the current landscape of telegenetics, various delivery models, and the number of programs utilizing videoconferencing for appointments (Terry et al., 2019). The authors surveyed different sites that defined themselves as telegenetics programs and found that 31% of respondents indicated they provided pediatric services by telemedicine, with only 6% including provider consults. Of the 51 self-defined telegenetics programs, 32 sites were using videoconferencing, 8 programs were using telephone technology, 2 programs reported the use of store-and-forward, and the remaining 9 programs were currently planning their programs to focus on the use of videoconferencing technology (Terry et al., 2019). While most refer to telegenetics as real-time videoconferencing appointments, it is important to note that telegenetics is an expanding field with a broad definition, similar to that of telemedicine and telehealth.

1.4 Telegenetics satisfaction

Numerous studies have reported high patient satisfaction with no significant difference between those patients seen by telegenetics and those seen in-person. Although a majority of the research has been conducted in a prenatal or cancer setting, all have had similar findings and have reported high patient and provider satisfaction (Buchanan et al., 2015; Cohen et al., 2016; Hilgart et al., 2012; Otten et al., 2016). In a review of telemedicine in genetics services, 14 articles reporting data from 12 different studies were analyzed to determine what conclusions can be drawn on the value of telegenetics; not only did all studies confirm previous reports of high levels of satisfaction, but they also

reported patients found telemedicine services to be valuable in receiving care (Hilgart et al., 2012). Where a comparison group was utilized, the level of satisfaction between the groups was not significantly different (Hilgart et al., 2012).

Pediatric telegenetics research has reported similar findings in the satisfaction of patients, pediatricians, and genetics providers (Hilgart et al., 2012; Hopper et al., 2011; Lea et al., 2005). Difficulty with persuading children to cooperate during a telegenetics visit has been referenced, yet this did not lower the overall reported satisfaction from the families surveyed (Hopper et al., 2011). Despite additional levels of complexity in a pediatric setting, which can include the need for children to cooperate when conducting a dysmorphology exam, all findings have been fairly consistent across the different specialties in genetics. This may be attributed to the perceived benefits of a telegenetics visit outweighing the challenges. A two year study on improving patient access by offering a telegenetics clinic in northwestern Florida found that 98% of patients strongly disagreed with preferring to wait for a face-to-face appointment (Stalker et al., 2006). In this same study, videoconferencing evaluations were able to decrease the wait time from 16.9 months to 3 months, which supports the overall benefits of telemedicine outweighing the limitations.

Additional qualitative studies have been conducted to address some of the initial concerns in the literature from many genetic counselors regarding the ability to effectively address psychosocial concerns through videoconferencing. Otten et al. (2016) conducted a study in the Netherlands looking at pre-symptomatic cardiac and cancer patients to further examine telegenetics counseling sessions that had taken place to the patient's home. They administered pre- and post-counseling questionnaires, which

revealed significantly higher satisfaction among those receiving counseling to the home and no significant difference reported in psychological outcome (Otten et al., 2016). This provides further evidence that the convenience and comfort of telegenetics visits to the home surpasses any limitations.

1.5 The use of telegenetics in pediatric genetics

Few studies have focused on the use of telegenetics in pediatric genetics evaluations. Of those reported, different delivery models were used in how the appointment was conducted, with a majority focusing on alternative models to improve timely access to genetics consultations and determine the effectiveness of telegenetics (Hilgart et al., 2012). One of the critical components for a pediatric evaluation includes a dysmorphology exam by a clinical geneticist. Questions have been raised about the effectiveness of a telegenetics evaluation in a pediatric setting where a physical exam is needed, and more research is needed on the diagnostic outcome. Of the few studies that have focused on the diagnostic effectiveness of a dysmorphology exam, minimal morphological findings were missed on a virtual exam, and no new diagnoses were made in-person that had not been identified during the telegenetics evaluation (Lea et al., 2005; Stalker et al., 2006). One study that included referring provider surveys did, however, find that one referring pediatrician noted that some dysmorphology features were missed in the telemedicine examination (Hopper et al., 2011).

Other studies have focused primarily on improving access to rural and underserved areas where there may be restricted access and maldistribution of genetics providers (Hopper et al., 2011; Kubendran et al., 2017; Lea et al., 2005). The ability to perform dysmorphology examinations from a distance is valuable in rapidly identifying

genetic conditions and improving timely access to genetic testing (Kubendran et al., 2017; Lea et al., 2005). Although this research suggests telegenetics as a viable solution in serving this patient population, it was not designed to evaluate the diagnostic yield for these pediatric patients.

The literature on the diagnostic efficacy of a pediatric telegenetics evaluation is scarce and the use of this modality seems to be underutilized in a pediatric setting. A recent study investigating the rapid implementation of telemedicine during COVID-19-related closures for a piloted program by the Division of Genetics and Metabolism at Children's National Hospital in Washington, D.C. provided initial data on visit numbers, types of diagnoses, and no-show rates before and during the 2020-2021 pandemic. As with many other telemedicine studies, common themes in their reason for investigation included minimizing delays in time from presentation to diagnosis (due to barriers in accessing genetic services), decreasing missed work, improving scheduling, and avoiding transport and exposure of medically fragile patients. Based on pre-COVID-19 and post-COVID-19 data, the demographics and types of diagnoses for their patients were very similar. Cited challenges included scheduling issues, technical problems, and licensure regulations that were most significant the first week of the transition. One limitation that is worth noting from this study was the accuracy of diagnostic decisions from telemedicine visits compared with in-person visits, with 50% of participating centers delaying scheduling or receiving results of investigational services (laboratory or radiological) and 31% of centers reporting manufacturer supply of specialized chemicals, kits, or consumables needed for diagnostic services was interrupted during the target period of this study. It was concluded that rapid implementation was a sustainable and

effective approach for delivery of services with high patient satisfaction rates. Despite positive feedback and beneficial outcomes, the researchers indicated future studies are needed in comparing diagnostic sequencing, biochemical testing, and hospitalization visit rates between patients seen by telegenetics to patients seen in-person (Shur et al., 2020).

With advancements in technology and an increase in the need for genetics services in underserved areas, it is important to identify how best to implement telegenetics in practice. Determining gaps, if any, in diagnostic outcome will be useful in developing well-defined guidelines and protocols in implementing telegenetics programs and alternative service delivery for patients and families.

1.6 Reimbursement for telegenetics services before COVID-19

One of the primary limitations affecting the implementation of telegenetics may be attributed to inadequate reimbursement from health insurers when compared to in-person evaluations. Much of the research conducted on large scale implementations of regional telegenetics programs was supported by funding or grants that enabled program development; however, all have cited continued funding as a limiting factor in the sustainability of telegenetics programs (Hilgart et al., 2012; Lea et al., 2005; Terry et al., 2019). Lower rates of reimbursement for telephone consultations have been reported by genetic counselors as an issue and is likely due to telehealth policies, where video consultations are eligible for insurance reimbursement, while telephone consultations are usually not (Terry et al., 2019). In one study, only 47% of video-capable programs billed insurance for services (Stalker et al., 2006; Terry et al., 2019).

While precise billing practices and reimbursement research in telegenetics is lacking, other specialties utilizing telemedicine have reportedly experienced similar

reimbursement issues. One study identified claims data from private insurers for mental health and substance abuse appointments by telehealth and found that the average reimbursement for appointments, which were based on diagnosis (ICD9) and procedure (CPT) codes, were half that of patients provided the same services in a face-to-face visit (Wilson et al., 2017). The results of the study imply that providers are less incentivized to offer or use telehealth even if it may improve patient outcomes, which reflects a similar theme in the literature about telegenetics programs.

In a 2012 systematic review reporting on research in 14 articles, none of the studies formally measured the cost or reimbursement of telegenetics services, despite citing that as a necessity in sustaining telegenetics programs in the future (Hilgart et al., 2012). It also concluded a need for telegenetics support from not only private insurers, but also Medicaid and Medicare. The demonstration of clinical effectiveness and improved patient outcomes is necessary to encourage reimbursement for all telegenetics services in the future (Hilgart et al., 2012).

While some private insurers have provided reimbursement for telehealth visits using live synchronous videoconferencing, it has historically been reimbursed at a lower rate than face-to-face visits. Centers for Medicare and Medicaid Services (CMS) has had strict requirements for telehealth eligibility, with federal Medicaid guidelines not recognizing telemedicine as a distinct service and only a small number of Medicare beneficiaries meeting the criteria to be eligible for telemedicine (Centers for Medicare and Medicaid Services, 2020). State Medicaid programs, on the other hand, vary in recognizing telehealth visits and providing reimbursement for services. This is important to acknowledge when considering the limitations of implementing telemedicine

programs. In 2017, one study concluded Medicare has a quantitatively substantial influence over private insurers' payment of services (Clemens & Gottlieb, 2017). Considering the influence Medicare has on private insurer coverage and reimbursement, the widespread expansion of telehealth services is unlikely without federal recognition and expansion of eligible telehealth services to be reimbursed at parity with in-person visits.

1.7 CMS: Expansion of telehealth following the public health emergency, COVID-19

Medicare and Medicaid telehealth reimbursement policy is typically made up of the following elements: where the patient is located during the telehealth visit, what modality is being used to deliver the telehealth services, who or what type of provider is delivering telehealth services, and what service is being delivered. The federal actions that have been made to telehealth reimbursement policy usually center on these four issues, which have largely expanded to accommodate more leniency during the public health emergency (PHE) during COVID-19. Consequently, a majority of these changes are temporary and need to be renewed before the expansion of these telehealth policy changes are set to expire, with the most recent renewal extending through the entirety of 2021 (Center for Connected Health Policy, 2021).

Inadequate reimbursement, or no reimbursement at all, has been previously reported as a challenge for healthcare systems looking to implement telemedicine as a service delivery model to improve patient access to genetic services (Hilgart et al., 2012; Terry et al., 2019). In response to the COVID-19 epidemic, CMS has temporarily expanded telehealth services eligible to patients. CMS has issued policy changes under the 1135 waiver which allows Medicare beneficiaries to receive a wide range of

telehealth services that were previously unavailable. For example, one major element that has allowed for expansion of services has been the temporary waiver of patient location by Medicare and Medicaid that has allowed patients to receive telehealth services to their home. Prior to the PHE, patients were limited to select sites that they would still have to travel to in order to be seen virtually by a provider in a separate location. Additionally, Medicare had separate geographic and service limitations that only covered select telehealth services to patients in rural locations. The Department of Health and Human Services (HHS) has issued recommendations under the 1135 waiver for the expansion of coverage for state Medicaid programs to give providers flexibility in service delivery to ensure Medicaid beneficiaries have access to care during the ongoing public health emergency (Centers for Medicare and Medicaid Services, 2020).

CMS has included the following statement on their website:

> Telehealth, telemedicine, and related terms generally refer to the exchange of medical information from one site to another through electronic communication to improve a patient's health. Innovative uses of this kind of technology in the provision of healthcare is increasing. And with the emergence of the virus causing the disease COVID-19, there is an urgency to expand the use of technology to help people who need routine care (CMS.gov, 2020).

Under these circumstances, it is critically important to fully evaluate the effectiveness of telehealth as a comparable alternative service to provide patients in the future, especially since the current expansion under the 1135 waiver is temporary, and

reimbursement, funding, and finances may once again serve as a barrier for telehealth despite the proposed benefits for patients.

With both federal and private insurance policies adjusting their coverage benefits to include and emphasize the use of telehealth for patient evaluations, we were able to study and compare patients seen in-person before the COVID-19 policy changes and after the restrictions were waived, allowing the increase of patients seen virtually. A quantifiable comparison is beneficial to the field of genetics to determine best practices in offering alternative methods to provide services to patients and consider the expansion of telehealth for genetic evaluations as a way to improve patient access. Many permanent changes have been made to CMS policy to expand telehealth coverage; however, for more widespread permanent changes to be made on the federal level, congressional action would be required. Therefore, it is necessary to quantifiably identify the similarities or differences in diagnostic outcome for patients who are seen virtually, as well as address additionally referenced advantages and limitations of telehealth services for patients. Furthermore, as COVID-19 has impacted patient contact and service delivery, it is important to identify if there are significant differences that should be addressed in future follow-up with patients seen virtually during this time.

1.8 Rationale of Study

Accessibility has been a widely reported issue across many medical specialties, and lower accessibility has been cited to include many factors such as provider shortages, patients living in rural or underserved geographic locations, transportation issues, inability to take time off work, etc. Telemedicine has been proposed as an alternative service to in-person evaluations to reduce this disparity and provide services to a larger

proportion of the population. Additionally, it has been utilized as an alternative method in seeing patients during the ongoing PHE, where limitations on non-emergency physical interaction has been recommended in order to prevent further transmission and spread of COVID-19.

Greenwood Genetic Center (GGC) has historically provided in-person evaluations by a clinical geneticist, but in response to the COVID-19 pandemic, GGC restricted in-person visits beginning on March 16, 2020, and transitioned to virtual visits (telemedicine to the patient's home) the week of March 30th. We evaluated new general genetics visits across three GGC offices in South Carolina and compared results between in-person (January and February 2020) and virtual visits (April and May 2020). The month of March was omitted due to transitioning all in-person appointments to virtual visits. Patient electronic medical records were reviewed to determine primary indication, testing ordered, and diagnostic outcomes.

Telemedicine is appealing to many clinicians that feel these services have the potential to minimize many of the current issues experienced by clinical genetics providers, including: no-show rates, wait times for an evaluation, and the direct and indirect costs to patients (travel time, taking time off work, etc). In fact, many of these benefits have been previously reported when patients are provided a telemedicine option, which has included an increase in efficiency, high patient satisfaction, decrease in wait times for an evaluation, and decrease in distance required for patient travel (Hilgart et al., 2012; Hopper et al., 2011; Lea et al., 2005; Stalker et al., 2006). However, much of the literature is lacking in analyzing differences and similarities by comparing in-person and pediatric telegenetic evaluations with a physical exam by a clinical geneticist. Therefore,

a quantifiable comparison is necessary to assess the similarities and/or differences in diagnostic outcome for patients who are seen by telemedicine when compared to those seen in-person. The aim of this study was to help provide a foundation in determining best practices in offering telegenetics as an alternative service delivery model and highlight considerations in the expansion of telegenetic evaluations as a way to improve patient access.

1.9 Objectives

1. Determine if there is a significant difference in diagnostic yield between pediatric patients seen by a clinical geneticist in-person when compared to patients seen by a clinical geneticist virtually by telemedicine to the patient's home.
    a. Analyze Clinical Assessment outcomes by comparing the number of patients with an outcome of: Clinical Genetic Diagnosis (met clinical criteria with/without the need for molecular confirmation), Environmental Etiology, Multifactorial Etiology, Isolated Anomaly, Within Normal Variation, and Testing Not Indicated
    b. For patients categorized as Testing Indicated within the Clinical Assessment outcome, identify and compare the diagnostic yield based on genetic testing results by ascertaining and categorizing results as Diagnostic, Undiagnosed, or Uncertain.
    c. Assess and compare the total number of in-person patients vs. telemedicine patients who received a diagnosis, either based on clinical assessment or genetic testing results.

2. Identify and compare the likelihood a diagnosis is made based on primary indication.
    a. Determine if providers were more or less likely to make a clinical diagnosis based on primary indication between in-person and telemedicine visits.
    b. Determine if providers were more or less likely to make a molecular/cytogenetic diagnosis based on primary indication between in-person and telemedicine visits.
    c. Evaluate if categorical primary indications (Neurodevelopmental Disorders, Structural Anomalies, Neurological Features, Additional Features, and Suspected Genetic Disorder/Known Family History of Genetic Disease) affected diagnostic outcomes and ensure populations were comparable in complexity.

1.10 Hypothesis

There will not be a significant difference in diagnostic yield between pediatric patients seen in-person when compared to those seen by telemedicine for a genetic evaluation. It is suspected that there will be differences in the likelihood a diagnosis is obtained based on primary indication; however, the variation of primary indications for patients will not differ between the telemedicine and in-person cohorts. Lastly, the testing strategy as well as the likelihood of second-tier testing and the number of those with a testing outcome categorized as Not Completed will vary between those seen in-person when compared to those seen by telemedicine.

CHAPTER 2

EFFICACY OF TELEGENETICS: A DIAGNOSTIC YIELD COMPARISON BETWEEN IN-PERSON AND TELEMEDICINE PEDIATRIC GENETIC EVALUATIONS[1]

[1] Merrihew, A., Lyons, M., Stallworth, J., Drazba, K., Abramson, R. To be submitted to Genetics in Medicine.

2.1 Abstract

The purpose of this study was to investigate the efficacy of telegenetic services for pediatric genetic evaluations conducted by telemedicine by comparing it to in-person pediatric genetic evaluations. Research into the utility of telegenetics would greatly serve to identify if this is a preferred alternative service delivery model to bridge the gap in accessibility and reach a greater catchment area of the population, especially to those living in underserved and rural locations. This study was a retrospective review of electronic medical records of pediatric patients seen at Greenwood Genetic Center (GGC) for initial in-person genetic visits prior to the COVID-19 pandemic and initial telemedicine genetic visits during the COVID-19 pandemic. Primary indications were reviewed in conjunction with the final clinical assessment made by the geneticist at the time of visit. Diagnostic information from the clinical assessment was used to determine if a clinical diagnosis could be made, which was categorized into clinical genetic diagnosis (met clinical criteria with/without the need for molecular confirmation), environmental etiology, isolated anomaly, multifactorial etiology, within normal variation, and testing not indicated. If testing was indicated, results were categorized into diagnosed, undiagnosed, uncertain, or not completed. Both clinical assessment and genetic testing outcomes were used in the diagnostic yield comparison. We found that visit type did not have a significant effect on the likelihood of diagnosis. Identifying the similarities in diagnostic outcomes for patients seen by telemedicine may strengthen the support for telegenetic services, improve accessibility to genetic services, and benefit both providers and patients.

2.2 Introduction

As the demand for genetic services continues to grow, it is imperative that genetic services are accessible to all patients seeking genetic evaluations, counseling, and appropriate genetic testing. As with many other healthcare services, the current demand far exceeds the number of qualified providers. This challenge, in conjunction with long wait times for appointments and oftentimes long distances to travel for patients seeking an appointment, need to be addressed with alternative service delivery models in order to ensure equity of care for underserved populations. Telemedicine has been suggested as one service delivery method proposed to remedy these challenges and the potential benefits of the use of telemedicine services has been an area of interest across all medical specialties. Continued research into the utility of telemedicine in genetics would greatly serve to identify if this is a beneficial alternative service delivery model to bridge the gap in accessibility and reach a greater catchment area of the population, especially to those living in underserved and rural locations.

With the recent outbreak of COVID-19, telemedicine has become a more common way to continue providing services to patients while minimizing the risk of disease transmission and maintaining social distancing recommendations. The Centers for Medicare and Medicaid Services (CMS) expanded coverage and reimbursement of telemedicine services to provide alternative appointment options for patients and providers so that they may comply with safety standards and social distancing recommendations, while maintaining the ability to offer clinical services to patients.

Research into the benefits and drawbacks for patients seen for a genetics evaluation by telemedicine will provide useful insight into who may best benefit from

this alternative service delivery model. Additionally, some providers have reported that their hesitancy in using telemedicine in genetics is the inability to pick up on psychosocial cues, visualize the patient clearly, and perform an adequate physical exam. However, many providers also report that the perceived benefits outweigh the concerns (Cohen et al., 2016; Hilgart et al., 2012). Due to clear and established genetic testing guidelines for children with neurodevelopmental delays, multiple congenital anomalies, and intellectual disabilities, it is assumed that the testing strategy would be similar regardless of being able to visualize the patient clearly. Alternatively, some providers may not rely so much on the physical evaluation for testing indications such as non-syndromic epilepsy, where previous imaging/testing such as an MRI or EEG may be more important in determining the best testing indicated. Clearly visualizing a patient and performing a physical exam, however, may be far more important in identifying easily recognizable genetic conditions where a clinical diagnosis can be made. It will be important to identify if the diagnostic outcome for patients seen by telemedicine and in-person is comparable given these previously reported concerns.

Our research aimed to provide insight for providers as a comprehensive comparison study of the diagnostic yield between in-person and virtual genetics visits via telemedicine. There have been many benefits previously reported when patients are provided a telemedicine option, which has included an increase in efficiency, high patient satisfaction, decrease in wait times for an evaluation, and decrease in distance required for patient travel (Hilgart et al., 2012; Hopper et al., 2011; Lea et al., 2005; Stalker et al., 2006). However, there is a lack of data comparing in-person and pediatric telegenetic (live video-conferencing to provide genetic services) evaulations with a physical exam by

a clinical geneticist. Furthermore, no published data have focused on the diagnostic outcome when a medical professional is not present to facilitate the use of videoconferencing technology for the patient or family to obtain the physical examination. Given the lack of literature examining the efficacy of telemedicine in comparison to in-person evaluations, this study generated quantifiable data to address if there are any significant differences in diagnostic outcomes between in-person and virtual visits. If a difference in diagnostic yield exists, it will be important to further examine who would most benefit from a virtual visit given there have not been guidelines established or best practices to adhere to when offering genetic services via telemedicine.

The goal of this research is to inform best practices moving forward, as it appears that telemedicine will remain a viable alternative method to provide care to patients. As with the goals stated in much of the literature and previous research, we aimed to investigate ways to improve access to genetic services, decrease the time from symptom onset to diagnosis, improve efficiency, reduce transportation and missed work barriers for caregivers, and provide quality care with high patient satisfaction. Due to the limited research comparing the efficacy and diagnostic outcome of telehealth visits to in-person evaluations, we explored pre-COVID-19 in-person data to compare with post-COVID-19 telehealth data. Not only is this an important area that has yet to be explored in the literature, it will largely determine best practices moving forward as genetic services continue to be offered to patients virtually. Additionally, the literature in genetic counseling services far outweigh the literature in genetic services that include a physical evaluation. It is critical to close the gaps in our current research regarding telemedicine

practices in clinical pediatric genetics by highlighting both the advantages and challenges of telegenetics.

Due to expanded coverage and reimbursement of telehealth services during the PHE, parity in reimbursement has allowed providers included in this study to continue seeing patients in a virtual capacity. This allowed us to compare populations seen by these providers in-person pre-COVID-19 to those seen by the same providers virtually post-COVID-19. Investigating the diagnostic yield has been an area that is continuously regarded as a need for future studies in determining telegenetics as an adequate alternative service delivery model. We hypothesized that there would not be a significant difference in diagnostic outcomes for patients seen in-person when compared to those seen by telemedicine. Therefore, our goal was to provide valuable insight in this area as we hope to minimize barriers to genetic services while providing data on efficacy and highlight what areas, if any, can be improved moving forward. Especially since reported patient satisfaction has been notably high for virtual visits and telehealth policy changes are beginning to catch up to technology, it is hard to imagine that telegenetics will disappear after COVID-19 public health emergency protocols are no longer in effect.

2.2 Methods

2.2.1 Participants

This study was a retrospective review of de-identified data from electronic medical records of patients seen at Greenwood Genetic Center (GGC). Two separate pediatric patient populations (<21 years of age) were analyzed: “Clinical New” patients seen in-person by a clinical geneticist during the two months prior to the implementation of virtual visits due to COVID-19 (January and February 2020) and then virtual visits, or

"Telehealth New" patients seen during the two months after the implementation of the PHE protocols (April and May 2020). A total sample population of 471 pediatric patients were analyzed in this study and categorized by visit type as either being in-person (IP) or telehealth (TH). The group sizes were unequal, with 240 IP patients and 231 TH patients. The goal was to determine diagnostic yield between the two patient populations. Multiple clinical geneticists across several GGC clinics who have seen patients in-person and virtually were included in the study for a total of six providers. Geneticists that either specialized in metabolic genetics or only see patients virtually were omitted from this study.

Patients seen in March 2020 were omitted from this study due to that month being a transition period when all in-person appointments were canceled and moved to virtual visits. Patients who were seen as a follow-up, by the metabolic clinic, by a non-geneticist, or who were over the age of 21 years were excluded from this study. If it had been more than 5 years since a patient had been seen by a clinical geneticist at Greenwood Genetic Center, they were considered a New patient and included in our analysis. Six patients of the 471 patients included had to be omitted, as they had been seen by genetics within the past 5 years.

Reports were generated from patient electronic medical records to include the following demographic information: visit type, no show visits, visit date, provider, patient age, patient zip code, patient sex, patient language, and patient race.

2.3.2 Primary Indication Categories

The referral indication with the primary clinical diagnosis was used to inform the selection of the Primary Indication for genetic evaluation. In cases where multiple

indications were included in the reason for referral, all clinical information was reviewed, including the primary diagnosis ICD10 code used by the geneticist, to ensure the primary indication was selected and categorized appropriately. If the indication for testing differed from the referral indication, the indication for testing was used as the primary indication. For patients who had testing completed before their visit, the Primary Indication was defined as "genetic testing completed prior to visit" and categorized as Suspected/Known Condition.

2.3.3 Phenotypic Categorization

Other features pertinent to whether testing was or was not indicated were categorized and recorded. This information included clinical features specifically noted by the geneticist either in the summary of the evaluation or as a primary feature on the test requisition. This phenotypic information was organized into 5 categories: Neurodevelopmental Disorders, Structural Anomalies, Neurological features, Additional Features, and Suspected/Known Condition. Neurodevelopmental Disorders included autism, developmental delay, fine motor delay, global delay, gross motor delay, learning delays/disability, speech delay, regression, and intellectual disability (based on intellectual quotient (IQ) scores below 70 or a clinical diagnosis if IQ unavailable). Structural anomalies included brain, cardiac/vascular, genitourinary/renal, craniofacial, eye, ear, musculoskeletal, gastrointestinal, integumentary: skin, integumentary: hair/nails, dental, and dysmorphic facies. Neurological features included abnormal muscle tone, abnormal movements, coordination/gait abnormalities, seizures, and neuromuscular problem. Additional Features included behavioral/psychiatric, cardiac (non-structural), endocrine, gastrointestinal, growth, hearing loss, hematologic, joint, metabolic measures,

ophthalmologic, prematurity/complications of prematurity, pulmonary/respiratory, renal/urinary, and other. Finally, the last category of Suspected/Known Condition included abnormal genetic testing prior to visit, family history of a known condition, and suspected recognizable genetic syndrome (or rule-out suspected condition). For a full list of conditions included in these categories, see Appendix A.

No additional clinical features were noted if prior testing was diagnostic and the patient was being seen to establish care or receive genetic counseling by the clinical geneticist; clinical assessment was therefore recorded and categorized as No Testing Indicated. If prior results were deemed uninformative or did not explain all the patient's features, those features were recorded and clinical outcomes were recorded appropriately based on the evaluation.

2.3.4 Clinical Assessment Categories

Patients were categorized into seven clinical assessment groups: Clinical Diagnosis Made, Environmental, Isolated Finding, Multifactorial, Testing Indicated, Testing Not Indicated, and Within Normal Variation. In cases where testing was not indicated due to the availability of another more appropriate/similarly affected family member, patients were placed in the Testing Not Indicated category. If such a patient was tested within a six-month timeframe to confirm or rule out a variant found on family member's testing, their categorization was changed to Testing Indicated and the outcome of the testing was recorded appropriately. For a full list of descriptive data that fall within each category, see Appendix B.

2.3.5 Genetic Testing Categories

The following testing types were included in this study: chromosome analysis, chromosomal microarray (CMA), *FMR1* repeat expansion, methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA), single gene analysis, single gene CytoScan Xon array (deletion/duplication analysis with increased coverage of disease-associated genes), next generation sequencing (NGS) multi-gene panel, CytoScan Xon array of a multi-gene panel, focused exome custom gene panel (including 2 or more genes by the ordering provider), focused CytoScan Xon array (including 2 or more genes by the ordering provider), whole exome sequencing (WES), and target analysis (including both targeted sequencing and targeted array). Biochemical testing was not included in this analysis unless it led to a molecular diagnosis, in which case the primary phenotypic indication for evaluation and testing was classified under "metabolic measures."

2.3.6 Diagnostic Outcome

For patients whose clinical assessment was Testing Indicated, records about the type of testing ordered and the results were reviewed. Due to the need to obtain insurance prior authorization for testing or other possible logistical delays, any genetic testing ordered at GGC within six months of the visit was analyzed. In the case of a sample failure requiring repeat collection and analysis, the timeframe to review the test results was extended to eight months. Any subsequent testing or second tier testing ordered within four months of the initial result return were also reviewed. No second-tier testing was reviewed after ten months from the time of the patient's initial visit.

Test results were categorized as follows: Diagnosed, Undiagnosed, Uncertain, and Not Completed. Diagnostic results included pathogenic, likely pathogenic, or variants of uncertain significance results that were determined to be clinically relevant to the primary indication. A likely pathogenic or pathogenic result with variable expressivity was also recorded as a diagnostic result. Undiagnosed patients had lab results that were either normal, included a secondary finding not relevant to the primary indication, or a result that was only felt to be partially clinically relevant. Uncertain results included variants of uncertain significance (VUS) that were either true uncertain variants or not felt to be clinically relevant VUSs. In cases where results could not clearly be categorized as diagnostic or non-diagnostic, clinical interpretation was ascertained from clinical or laboratory documentation within the patient's electronic medical record, such as in the case of a VUS felt to be causative, or a pathogenic alteration in a gene associated with a condition not relevant to the primary indication. If there was no documentation by the ordering provider indicating a strong suspicion that a VUS was felt to be clinically relevant or felt to not be clinically relevant to the patient's features, the results were classified simply as unknown significance under the Uncertain category.

Lastly, if testing was indicated but the patient's sample was not returned, there was an insurance coverage-related issue, a parent/guardian deferred testing, the provider deferred testing, sample failure occurred, or a patient was lost to follow-up, they were categorized as "testing was not completed" category. For a full list of descriptive data that falls within each category, see Appendix C.

2.3.7 Statistical Analysis and Statistical Methods

For patient records that met the inclusion criteria during the timeframe studied, 240 consecutive new in-person patient visits conducted during the months of January and February 2020 were reviewed and 231 consecutive new virtual visits during the months of April and May 2020 were reviewed. Patient records were reviewed to collect relevant clinical, medical, and laboratory data including the primary indication, phenotype, clinical assessment, genetic testing, and diagnostic outcome. Categorization was made based on clinical and laboratory documentation in the medical records. Collected information was used to determine relationships between the two groups (in-person visits and telehealth visits), ensure groups are comparable in complexity, and investigate any significant correlations that may impact the results identified in our primary objectives.

Categories were analyzed to determine if the presence of any of these features were more likely to be associated with a diagnosis, as well as ensure that the study groups had a similar distribution of primary indications for genetic evaluation. For patients that did not have genetic testing, Clinical Assessment was used to determine the likelihood a clinical diagnosis could be made with the results used to compare the patient populations analyzed.

A database in Microsoft Excel was used to store data obtained from the patient chart abstractions. Categorical data from patient electronic medical record were coded and recorded into the Excel database to the corresponding patient. This was completed by the same individual for all patients included in this study to ensure consistency. Once completed, de-identified data were exported to IBM Statistical Package for Social Sciences (SPSS) for quantitative analysis. Descriptive statistics, using percentages and

frequencies, were calculated based on the collected categorical data. Pearson's Chi-square Test of Homogeneity was used to compare variables and statistical significance was determined from a two-tailed exact value. A two-tailed T-Test was used for quantitative analysis to compare ages of patients included in the study. Figures and tables were constructed using SPSS and Microsoft Excel.

2.4 Results

Based on the clinical assessment conducted by a clinical geneticist, 70 patients (14.9%) received a clinical diagnosis based on exam, and 56 patients (11.9%) received a diagnosis based on genetic testing that was ordered following a clinical examination. One hundred and twenty-six patients (26.75%) in total received a diagnosis either based on clinical examination or through genetic testing. The outcome for all patients can be seen in Figure 2.1.

Demographic information was ascertained and used for analysis to determine variations between the patients seen by TH when compared to those seen IP. The information that was abstracted for review included Age, Gender, Race, Ethnic group, and Primary Indication (Table 2.1).

An independent-samples t-test was run to determine if there were differences in the mean ages of pediatric patients based on visit type. Age ranges were normally distributed, and there was homogeneity of variance, as assessed by Levene's test for equality of variances ($p = 0.204$). The mean age of IP patients ($M = 4.35$, $SD = 4.715$) was less than the mean age of TH patients ($M = 4.65$, $SD = 5.253$), though no statistically significant difference was found between the two populations, $M = 0.291$, 95% CI [-1.19, 0.61], $t(469) = 0.204$, $p = 0.527$.

A Chi-square test of homogeneity was conducted between visit type to determine statistical significance within the ascertained demographic categories. Patient counts for each category as well as corresponding statistical analysis can be seen in Table 2.1. With expected cell counts that were less than five in Race and Ethnic Group categories, Egon Pearson N-1 Chi-square corrected test was conducted to analyze differences between visit types. Statistical significance was determined for Ethnic Group ($N - 1\ \chi^2\ (1) = 8.995$, $p = 0.003$), as assessed by N-1 Chi-square test.

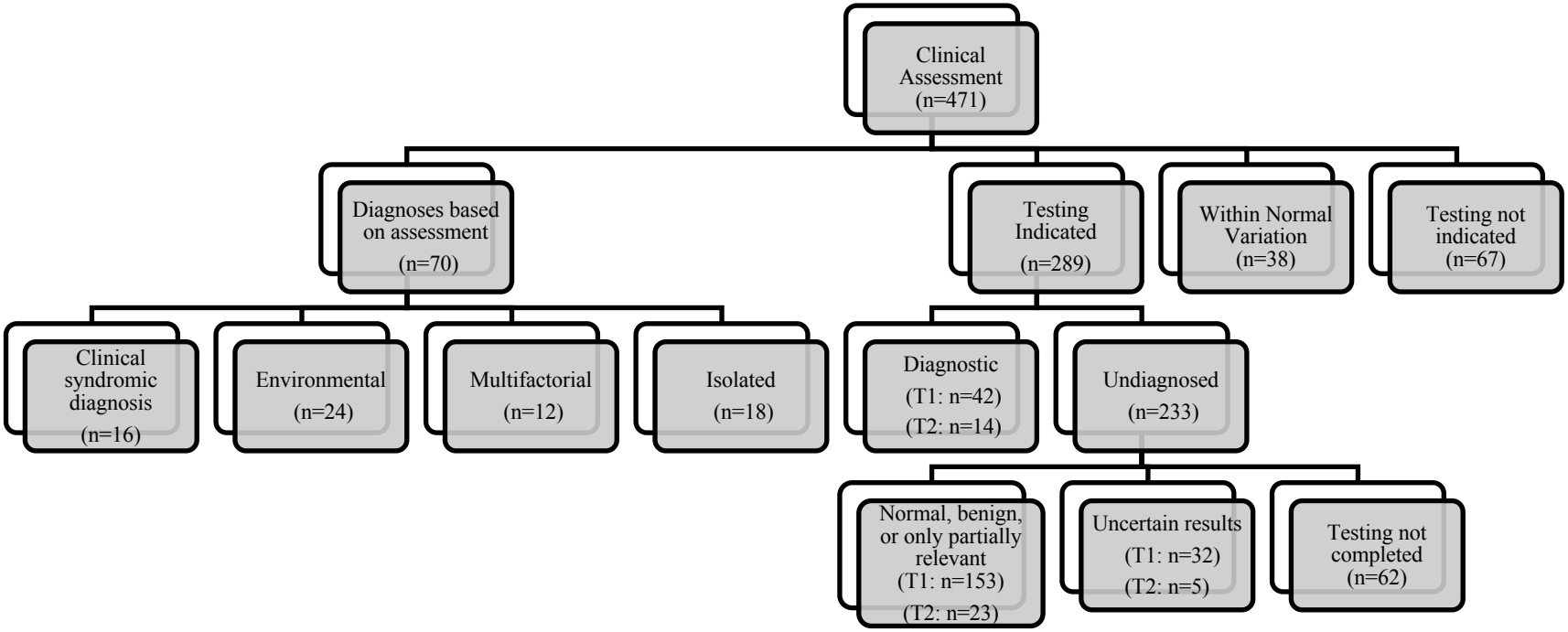

Figure 2.1 *Outcomes for all 471 patients included in this study. Testing outcomes were split up between the number of patients with the corresponding outcome found on Tier 1 (T1) testing or Tier 2 (T2) testing.*

Table 2.1 Comparison of demographic data between IP and TH patients

Characteristic	Visit Type		Overall Sample	Statistical Analysis N=471
	In-Person	Telehealth		
Age in Years *M (SD)*	4.35 (4.72)	4.65 (5.25)		t(469) = 0.633 p = 0.527
Gender *n (%)*				
Male	157_a (54.1)	133_a (45.9)	290 (61.6)	χ^2 (2) = 3.058
Female	83_a (45.9%)	98_a (54.1)	181 (38.4)	p = 0.08
Ethnic Group *n (%)*				
Non-Hispanic or Non-Latino	208_a (86.7)	221_a (95.7)	429 (91.1)	χ^2 (2) = 12.96[a] p = 0.002
Hispanic or Latino	30_a (12.5)	8_b (3.5)	38 (8.1)	
Refused/Declined	2_a (0.8)	2_a (0.9)	4 (0.8)	
Race *n (%)*				
Asian	5_a (2.1)	2_a (0.9)	7 (1.5)	χ^2 (6) = 18.409
Black or African American	41_a (17.1)	52_a (22.5)	93 (19.7)	p = 0.005
Hispanic	29_a (12.1)	7_b (3.0)	36 (7.6)	
White or Caucasian	151_a (62.9)	147_a (63.6)	298 (63.3)	
Biracial or multiracial	6_a (2.5)	9_a (3.9)	15 (3.2)	
Other	1_a (0.4)	3_a (1.3)	4 (0.8)	
Unknown	7_a (2.9)	11_a (4.8)	18 (3.8)	
Clinical Indication for Genetic Evaluation *n (%)*				
Neurodevelopmental Disorders	122_a (51.9)	127_a (55.2)	249 (52.9)	χ^2 (4) = 4.361 p = 0.359
Structural Anomalies	39_a (16.6)	34_a (14.8)	73 (15.5)	
Neurological Features	16_a (6.8)	8_a (3.5)	24 (5.1)	
Additional Features	19_a (8.1)	26_a (11.3)	45 (9.7)	
Suspected/Known Condition	39_a 16.6)	35_a (15.2)	74 (15.7)	

Corresponding statistical analysis per comparison is located in the far-right column, with statistically significant differences identified between the two populations based on Timing of Visit ($p < 0.001$), Ethnic Group ($p = 0.002$), and Race ($p = 0.005$).

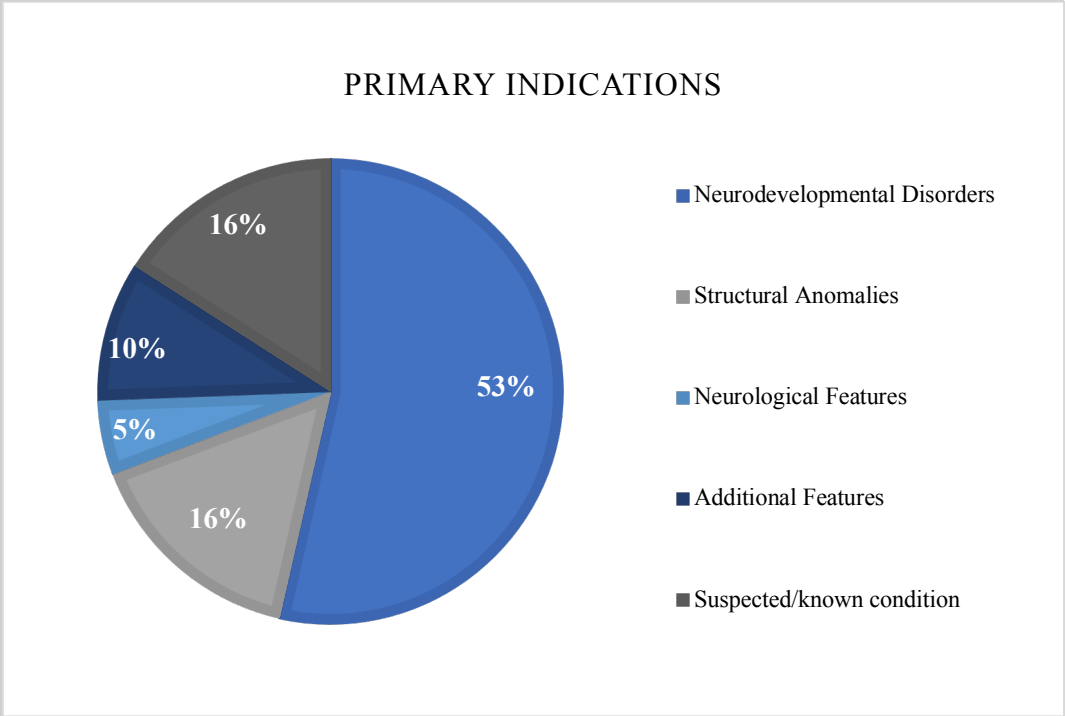

Figure 2.2 *Total percentage of patients seen for a genetic evaluation based on indication*

Primary patient indications were additionally analyzed to determine the proportions of broad indication groups and clinical assessment outcomes. The proportion of patient indications found in each clinical assessment category was determined to be significant, $p < 0.001$. The distribution of patients found in each category can be seen in Figure 2.3. Descriptive data regarding the differences in outcomes based on phenotypic indications can be found in Appendix B.

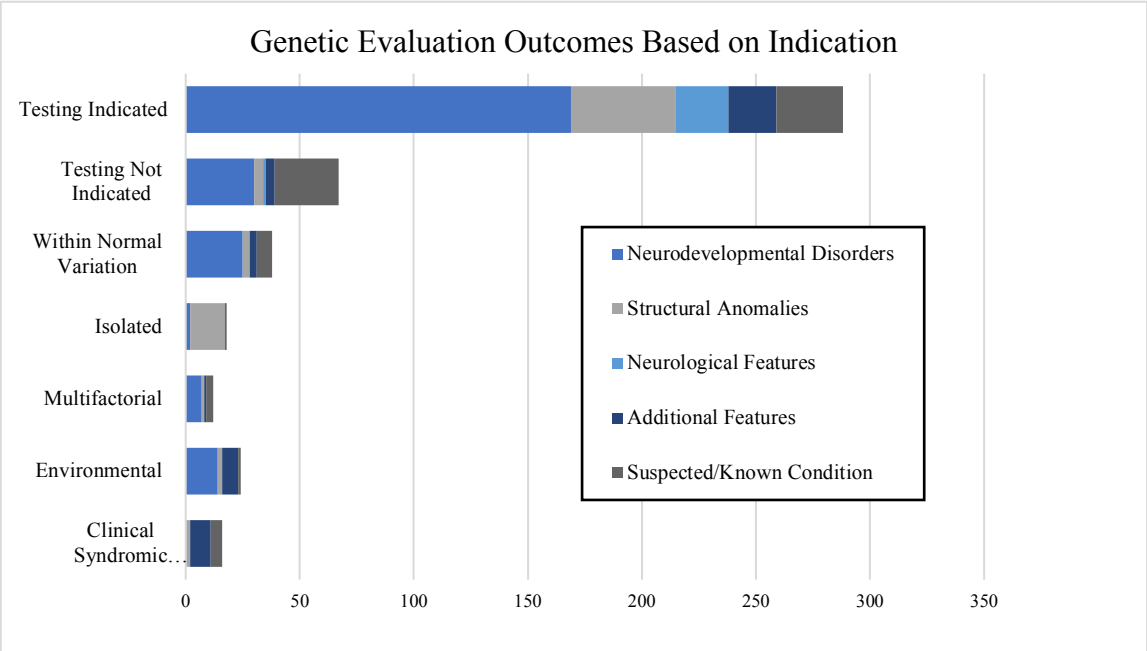

Figure 2.3 *Clinical assessment outcomes based on patient primary indication*

Further assessment in comparing patients' primary indication categories and genetic testing outcomes identified a statistically significant difference in proportions, as assessed by Chi-square test of homogeneity, $p = 0.001$ (Table 2.2). Statistical significance was determined with corrected values ($N - 1$ $\chi^2 = 13.285$, $p < 0.001$). Diagnostic yield for each of the primary categories was determined. Statistical significance was observed for two of the primary indications that received a diagnostic result from genetic testing: Neurodevelopmental Disorder and Suspected/Known Condition. Twenty-five patients (44.6%) out of the total 56 patients who received a diagnosis based on genetic testing had a primary indication of Neurodevelopmental Disorder, which was lower than the expected diagnostic outcome (15.0% vs. 19.4%). The other primary indication that was determined to have a statistically significant diagnostic yield was in the Suspected/Known Condition category, where 15 patients (26.8%) out of the total 56 patients received a diagnostic outcome based on testing, which was higher than the

expected outcome (46.9% vs. 19.4%). Additional diagnostic testing yield based on indication can be seen in Table 2.2.

Table 2.2 Diagnostic Yield Outcomes Based on Patient Primary Indication

	Diagnostic Testing Results			
Primary Indication Category	Not Diagnostic N= 233 (80.6)	Diagnostic N=56 (19.4)	Total Sample N=289	Pearson Chi-Square N=289
Neurodevelopmental Disorders *n (%)*	142_a (85.0)	25_b (15.0)	167 (57.8)	χ^2 (4) = 18.157 p= 0.001
Structural Anomalies *n (%)*	39_a (84.8)	7_a (15.2)	46 (15.9)	
Neurological Features *n (%)*	18_a (78.3)	5_a (21.7)	23 (8.0)	
Additional Features *n (%)*	17_a (81.0)	4_a (19.0)	21 (7.3)	
Suspected/Known Condition *n (%)*	17_a (53.1)	15_b (46.9)	32 (11.1)	

Differing subscripts denote statistically significant differences. NDD were found to have a diagnostic yield statistically significantly lower than expected. Suspected/Known Conditions were found to have a diagnostic yield statistically significantly higher than expected yield. No statistical significance was detected in remaining indication groups.

To determine variations in clinical assessment outcomes, a corrected *N*-1 Chi-square (2 x c) was conducted between visit type and the outcome of the genetic evaluation clinical assessment, with two expected cell counts less than five. Statistical significance difference in proportions, as assessed by *N*-1 Chi-square test, $p < 0.001$, was found in two out of the seven clinical assessment categories (Table 2.3). The proportion of patients classified as having an isolated feature or as being within normal variation was

statistically significantly lower in the telehealth population, $p < 0.05$. The proportion of patients in all remaining categories were not found to be statistically significant.

Patients were determined to have a diagnosis of an isolated feature in 15 patients (83.3%) with an in-person visit compared to 3 patients (16.7%) with a telehealth visit. In the patient population determined to be within normal variation based on clinical assessment, 27 in-person patients (71.1%) were identified compared to 11 telehealth patients (28.9%).

Table 2.3 Clinical assessment outcomes found in both IP and TH patient population

Clinical Assessment Outcome	Visit Type		Total Sample N=464	Chi Square N=464
	In-Person N= 235	Telehealth N=229		
Clinical Diagnosis of Genetic Condition *n (%)*	7_a (3.0)	9_a (3.9)	16 (3.4)	$\chi^2(6) = 19.97$ $p = 0.003$
Environmental Etiology *n (%)*	15_a (6.4)	9_a (3.9)	24 (5.2)	
Multifactorial Etiology *n (%)*	4_a (1.7)	8_a (3.5)	12 (2.6)	
Isolated Feature/Anomaly *n (%)*	15_a (6.4)	3_b (1.3)	18 (3.9)	
Within Normal Variation *n (%)*	27_a (11.5)	11_b (4.8)	38 (8.2)	
Testing Not Indicated *n (%)*	28_a (11.9)	39_a (17.0)	67 (14.4)	
Testing Indicated *n (%)*	139_a (59.1)	150_a (65.5)	289 (62.3)	

The percentages, as seen in parentheses, indicated the percentage of the total visit type populations (IP, TH, or of the total sample size). Chi square testing was used to determine significance. Differing subscripts indicate the outcomes with statistically significant difference in values, as seen in Isolated Feature/Anomaly and Within Normal Variation.

The overall clinical diagnostic yield, based on patients who had clinical assessment outcomes categorized as Clinical Diagnosis Based on Exam, Environmental Etiology, Multifactorial Etiology, or Isolated Feature were analyzed to determine percentages in TH and IP clinical diagnoses. The total number of patients receiving a clinical diagnosis was 70 out of the 464 patients included in this study for an overall diagnostic yield of 15.1%. The number of patients seen in-person that received a clinical diagnosis was 41 out of a total of 235 patients, resulting in a 17.5% yield. In comparison, 29 patients seen by telehealth were found to have a clinical diagnosis out of a total of 229 patients, resulting in a 12.6% diagnostic yield.

Of the clinical assessment outcomes, Isolated Feature/Anomaly and those found to be Within Normal Variation were diagnosed in a significantly higher number of IP patients in comparison to patients seen by TH.

Descriptive details, which can be found in Appendix B, found that IP patients with a clinical assessment outcome of Isolated Feature/Anomaly had a majority of primary indications falling in the Structural Anomaly category, with most patients identified to have Craniofacial Anomalies (6), followed by Structural Heart Anomaly (2) and Gastrointestinal Anomalies (2). In total, 15 patients in the IP population were diagnosed with an Isolated Feature/Anomaly, 13 of which had a primary indication classified as Structural Anomaly. The other patient had a primary indication of a Recognizable Genetic Condition, specifically to rule out McCune-Albright syndrome but was found to have isolated precocious puberty due to ovarian cysts. In comparison, only three total TH patients received a clinical diagnosis of Isolated Feature. One patient with a primary indication of Neurodevelopmental Disorders had developmental delay that was

documented by that provider to be a result of benign enlargement of subarachnoid space (BESSI)-related macrocephaly. The other two patients were categorized to have Structural Anomalies, specifically Structural Heart Anomaly.

A majority of patients that were felt to be Within Normal Variation were identified to have Neurodevelopmental Disorders in both IP (19/27 patients, 70.4%) and TH (6/11 patients, 54.6%) visits. About half of the IP patients with a Neurodevelopmental Disorder had Developmental Delay (9/27 patients; 33.3% of the total), while the others had Speech Delay (10/19 patients; 37.0% of the total). This distribution was similar in the TH patients as well, with half of the patients having Developmental Delay (3/11 patients; 27.3% of the total) and the other half having Speech Delay (3/11 patients; 27.3% of the total). The next most common indication present in the IP patients found to be Within Normal Variation was identified in patients with Additional Features; specifically, those classified as having Joint Problems (3/27 patients; 11.1%). Upon clinical assessment, these patients were not found to meet criteria for hypermobile Ehlers-Danlos syndrome (hEDS). Only one patient with Joint Problems in the TH patient population was felt to be Within Normal Variation for this same reason (1/11 patients; 9.1%). Interestingly, the TH population with a primary indication of Joint Problems was observed more in Clinical Diagnosis category with a diagnosis of benign joint hypermobility syndrome; a total of five patients (5/9 patients; 55.6%) fell into this clinical assessment outcome. In addition, one patient with an indication of Recognizable Genetic Condition received a clinical diagnosis of benign joint hypermobility syndrome after hEDS was ruled out on exam. In comparison, only three IP patients received a

clinical diagnosis for Joint Problems (3/7 patients; 42.9%). More details regarding descriptive details of the clinical assessment can be found in Appendix B.

In the 38 total patients identified that were found to be within normal variation, 65.8% had a primary indication of Neurodevelopmental Disorder, with a higher number of IP patients receiving this clinical outcome (19/38 IP patients vs 6/38 TH patients).

The primary indications of patients who were categorized as Testing Indicated or Testing Not Indicated were not analyzed because no differences were observed in those assessment outcomes between the TH and IP populations.

Genetic testing was indicated in a total 289 patients, with 139 IP patients and 150 TH patients. The distribution of this group can be seen in Figure 2.1. Additional analysis using Chi-square test of homogeneity was used to compare testing outcomes between IP and TH patients. Note that only 227 patients were analyzed, as 62 patients failed to complete testing (35/62 TH patients, 27/62 IP patients). Analysis of tier 1 testing outcomes found there to be no statistically significant differences in the proportions of patients who received a diagnostic, non-diagnostic, or uncertain result based on testing performed in patients seen in-person when compared with those seen by telehealth, $p = 0.938$. Of the 227 patients who had genetic testing, a total of 42 patients were found to have an underlying genetic cause for their features for a tier 1 diagnostic yield of 18.5%. Twenty-one of those patients were seen by TH (18.4% TH diagnostic yield) and twenty-one patients were seen IP (18.6% IP diagnostic yield). Similarly, the same analysis was performed for tier 2 testing in those patients who remained undiagnosed following tier 1 testing ($n = 42$). Statistical significance was not identified in the proportion of patient testing outcomes when comparing patients seen IP to those seen by TH (Figure 2.4). The

diagnostic yield for patients receiving tier 2 testing was 31.8% TH compared to 35.0% IP. Additional testing details regarding test strategy and descriptive data based on phenotypic descriptions in each primary indication group can be found in Appendix A and D.

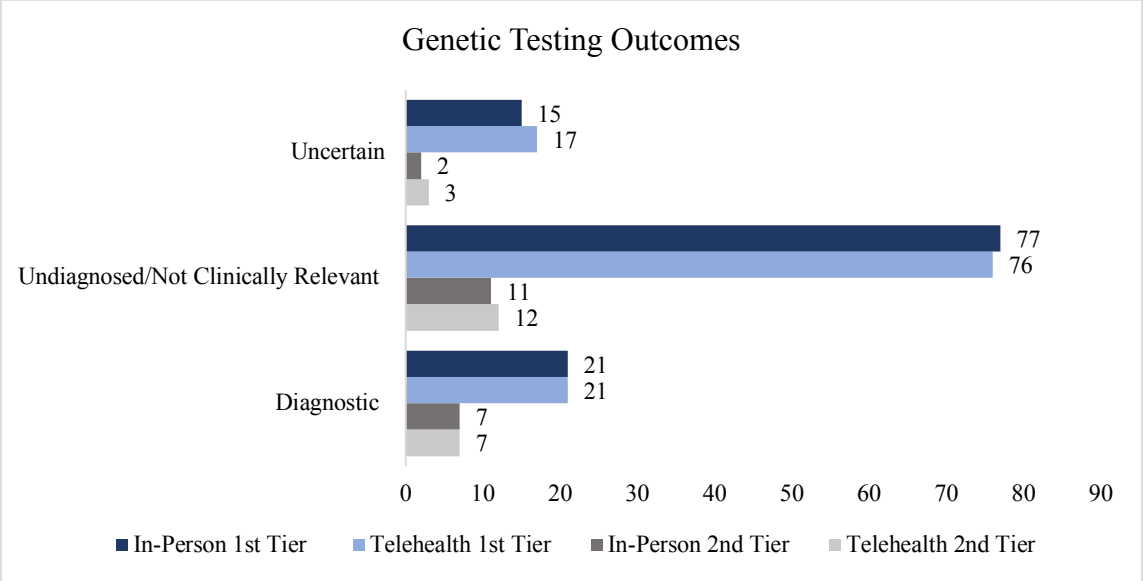

Figure 2.4 *Genetic testing outcomes as determined by either first or second tier tests.*

Patients who received either a clinical diagnosis based on exam or received a diagnostic result following genetic testing were reviewed to determine the overall diagnostic rate for patients seen in-person compared to patients seen by telehealth (Figures 2.5 – 2.6). The overall diagnostic yield for both groups was 27.1%, with the in-person diagnostic yield being 29.2% and telehealth diagnostic yield being 24.9%. There was no statistical significance between IP and TH patient populations regarding the overall diagnostic yield, as assessed by Chi-square test of homogeneity, $p = 0.292$.

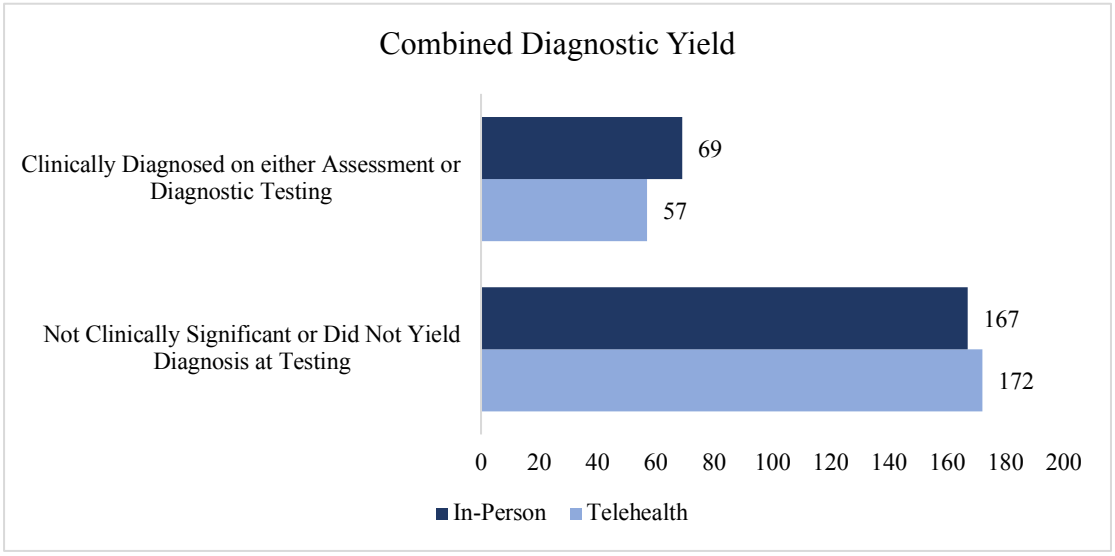

Figure 2.5 *Comparison of IP and TH patients based on the combined diagnostic yield to include diagnoses made by clinical exam or diagnostic testing.*

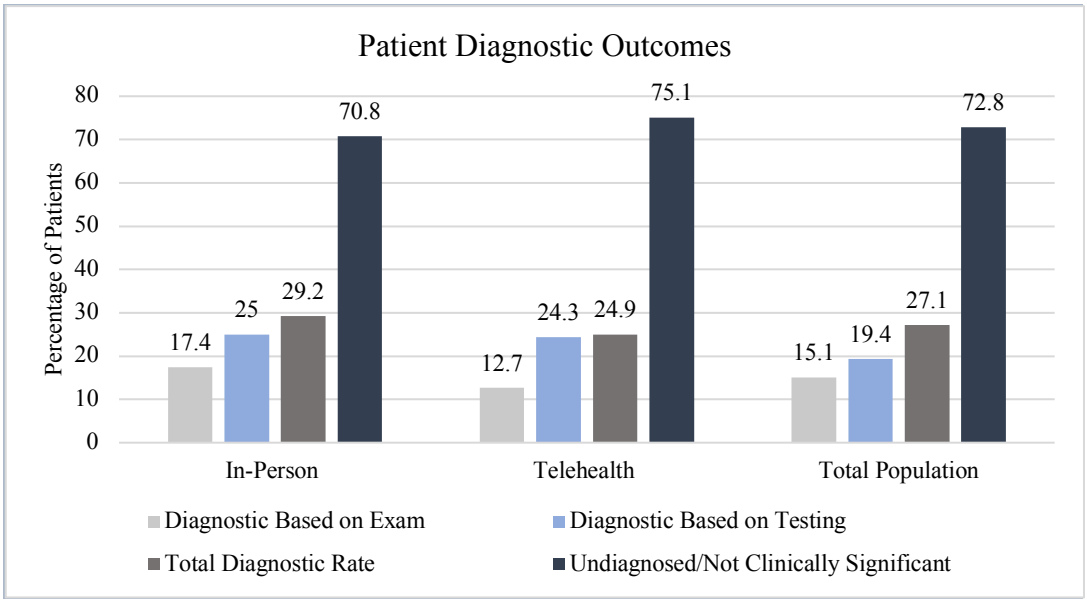

Figure 2.6 *Comparison of the percentage of IP, TH, and total patient population and corresponding diagnostic outcomes.*

2.5 Discussion

2.5.1 Demographic Differences

To determine if the diagnostic testing outcomes were truly not statistically significant, due to either differences in patient demographics or indications for a genetic evaluation, we further investigated variations between the in-person and telehealth populations. Age groups, gender, and clinical indications were not significant when comparing the two types of visits. There was, however, a significant decrease in patients who reported their ethnicity as Hispanic/Latino that were seen by TH when compared to IP (TH = 3.5% vs. IP = 12.5%, $p = 0.002$). Unsurprisingly, this difference was also identified in the patient's reported race, with 12.1% of those identifying as Hispanic seen by an in-person evaluation, and 3.0% of those identifying as Hispanic seen by a telehealth evaluation ($p = 0.005$). Non-Hispanic or Non-Latino patients as well as all other races included in this study were comparable between the two groups.

Although we did not investigate details to support this theory, the smaller number of Hispanic patients seen by telehealth may in part be due to challenges in incorporating an interpreter into a telehealth visit, as opposed to a technology barrier within this ethnic group. GGC has historically utilized in-person interpreter services during in-person appointments; however, non-urgent appointments requiring translation services were temporarily put on hold during the transition of all in-person visits to telehealth visits in the COVID-19 pandemic to allow providers to get acclimated to telehealth. Since the transition, interpreter services can be used during virtual visits but there are logistical challenges so IP visits are typically preferred. Further investigation into the underlying barriers leading to discrepancies due to demographics as it pertains to the Hispanic or

Latino population may help elucidate the reasons behind this variation. Additionally, once identified, it would provide new insight into whether this is a result of a lower uptake of telemedicine services based on race or ethnicity or if this variation is the result of clinic-driven procedures. Identifying and reducing the underlying barriers would serve to better provide equitable telehealth services to the Hispanic or Latino population.

No significant difference was found in the distribution of primary patient indications seen by TH when compared to those seen IP. The importance of the inclusion of this analysis was that we did identify significant difference in clinical assessment outcomes as well as diagnostic yield based on indication. A clinical diagnosis of an Isolated Feature/Anomaly was more likely to be given in the IP cohort. Additionally, we determined that a majority of the patients with isolated features were categorized as having a primary indication of Structural Anomaly. Given the distribution of patients seen with a primary indication of Structural Anomaly (16.6% IP vs 14.8% TH) was not significantly different, we can infer that it is unlikely that the discrepant Isolated Feature/Anomaly diagnosis based on clinical assessment is attributed to unequal distribution of a primary indication of structural anomalies in each visit type, though one cannot entirely rule it out given our population size.

Similarly, with the difference seen in TH and IP patients who were determined to be within normal variation based on clinical assessment, we can infer this was not a consequence of unequal distributions of patients based on primary indication. The difference in TH and IP clinical assessment outcome found to be within normal variation, may in part be due to provider comfort in making this call without seeing the patient for an IP physical examination. Further research may be needed to determine if the decrease

in this clinical assessment outcome in the TH population is uniform across all providers, or if this may be more common in some providers over others. Additionally, this could be an area of interest in creating telemedicine workflows, protocols, and training aimed at minimizing differences seen in clinical assessment outcomes between IP and TH visits.

2.5.2 Outcomes based on clinical assessment

The goal of this study was to evaluate any difference in diagnostic outcomes for patients seen by telehealth when compared to those seen in-person. Much research has been done to assess and compare provider and patient satisfaction rates between telemedicine and in-person evaluations. Stalker et al. (2006) determined some of the provider concerns in utilizing telemedicine, specifically, as it pertains to being able to perform an adequate clinical evaluation to make a diagnosis based on phenotypic findings. For that reason, we analyzed the patient outcomes of clinical assessments done in-person and compared them to those done by a telehealth visit.

The overall clinical diagnostic yield, based on patients who had clinical assessment outcomes categorized as Clinical Diagnosis Based on Exam, Environmental Etiology, Multifactorial Etiology, or Isolated Feature were analyzed to determine percentages in TH and IP clinical diagnoses. We saw a different clinical diagnostic yield between the IP and TH groups. While this difference was not statistically significant, we thought of several reasons as to why these numbers may vary. One of these reasons is that multiple providers were included in this study and provider documentation was relied on to determine the categorization of the evaluation outcome. Therefore, differences in provider-specific diagnostic yield and clinical assessment outcomes may have contributed to the differences seen in assessment outcomes. It is also important to

consider that some providers may have not seen an equal proportion of TH patients following the transition from IP visits.

The differences observed in Isolated Features between the two populations may be the result of difficulty distinguishing a feature as isolated without an in-person examination. Phenotypes within the Structural Anomaly category, such as congenital heart defects (CHD) or other major malformations, may be easier to report as isolated in the absence of other malformations, dysmorphism, or family history; however, this may be more difficult to determine without an in-person physical examination for patients with minor anomalies (e.g. ear tags, cleft lip +/- cleft palate, etc). Additionally, many isolated anomalies are felt to be multifactorial and therefore would be provider-dependent on whether it is documented as isolated vs. multifactorial. The lower number of TH patients categorized as having isolated features based on clinical examination may have signified that providers were more willing to pursue genetic testing to rule out genetic etiology as opposed to relying on a virtual examination. Although we investigated the diagnostic yield as it pertains to primary indication, we did not explore differences in testing strategies based on indication in the IP and TH populations.

Future studies could seek to identify if the slight increase in number of TH patients who were found to have either testing indicated, or not indicated were due to a higher number of patients with Neurodevelopmental Disorders receiving either of these clinical assessments. It may be that a provider was more likely to determine Testing Not Indicated for reasons that are described as Wait-and-See Approach, as described in Appendix C. It could also be that a provider feels more comfortable following-up to ensure developmental progress is made, rather than documenting whether or not they felt

the patient fell in the Within Normal Variation category. Given our TH population was ascertained in the immediate two months following the onset of the PHE, these patients may have had developmental therapies interrupted, thus making it more difficult to determine if developmental progress had been made.

It is unclear if variations observed between the two patient populations as a consequence of our population size, different testing strategies based on clinical indication, provider differences in documentation, or if this is a result of previously mentioned trepidation amongst providers in performing a clinical evaluation by telehealth (Hilgart et al., 2012). In the study by Lea et al. (2005), familiarity and comfort with telemedicine technology was a way to improve provider confidence in offering telegenetic services. This may be an interesting area to expand on in future research.

2.5.3 Genetic Testing Outcomes

As expected in our hypothesis, we did not identify a difference in diagnostic yield of genetic testing for patients that were seen in-person prior to the COVID-19 public health emergency protocols when compared to the patients who were seen after the transition to seeing patients virtually.

Given the distribution of primary indications for patients that were seen by telehealth and in-person were similar, we can infer that this outcome is not an artifact of uneven distribution of patients with an indication that would have a significantly higher yield of a diagnostic outcome in one group over the other.

Our results were consistent with previous studies analyzing the diagnostic yield of genetic testing in patients with a variety of phenotypic indications. For both populations that were compared in our analysis, our diagnostic outcomes (~18.5%) were similar to

those previously observed around 15-20% in patients with indications including MCA, DD/ID, and ASD (Miller et al., 2013). Similarly, tier 2 testing in our patient population had an overall diagnostic yield of 33.3%, which is consistent with literature suggesting that a diagnostic yield may be as high as 40% in those with a targeted sequencing approach following exam, testing performed in those with a family history suggestive of a genetic diagnosis, or tier 2 testing in those whose initial testing fails to identify an underlying genetic cause (Kiely et al., 2016).

These data support our hypothesis and suggest that a pediatric genetic evaluation performed by telehealth is as effective in determining a diagnostic outcome from a testing perspective.

2.5.4 Combined Diagnostic Yield

Although a statistically significant difference was found in two of the seven possible clinical assessment outcomes, this did not impact the final combined diagnostic yield (clinical diagnostic outcomes and genetic testing outcomes) in comparing IP and TH patients. No statistical significance was determined; however, a slightly higher number of IP patients received a diagnostic outcome (69 patients; 14.8%) when compared to the TH population (57 patients; 12.3%). This outcome is consistent with our hypothesis that a statistically significant difference would not be found between patients seen IP when compared to those seen by TH. Previous studies that have reviewed the diagnostic effectiveness resulting from a video-conference telegenetics examination in the pediatric setting support that it is unlikely that a provider would miss a diagnosis based on different modalities alone (Lea et al., 2000; Stalker et al., 2006). Our results suggest that it is unlikely a diagnosis would not be made solely based on the patient's

visit-type; however, a provider may be less likely to definitively document whether or not a patient's features are within normal variation or felt to have no underlying genetic etiology when not undergoing a physical examination in-person.

2.5.5 Telehealth as an Alternative Service Delivery Model

The primary goal of this study was to determine if telehealth is an adequate alternative service delivery model for pediatric patients receiving clinical genetic evaluations. With the previously mentioned barriers such as distance to provider, travel distance, financial burdens, including missed work and childcare for other children, as well as the addition of COVID-19-related barriers, finding opportunities to make genetic services more accessible is a primary focus. With our results identifying similar overall diagnostic outcomes for both telehealth and in-person pediatric genetic evaluations, it would be reasonable for institutions to consider telegenetic evaluations as a comparable alternative to an in-person genetic evaluation.

This study found no difference in diagnostic yield between TH and IP visits; however, larger studies in the future could provide additional support for our findings. Further investigation into the discrepancies in clinical diagnoses may provide valuable insight into the differences identified in this study. Given differences in testing outcomes were not observed but differences were observed in some of the clinical assessment categories, identifying patients who are most likely to have testing indicated prior to their visit may allow those patients to be scheduled for a telemedicine evaluation due to similarities found in diagnostic testing yield. An in-person evaluation, however, may be more beneficial to patients whose clinical evaluation or physical examination would determine whether or not they will receive a clinical diagnosis or if they will be found to

have testing indicated. For patients with a primary indication with an expected high diagnostic yield based on testing, and a low clinical diagnostic yield (e.g. patients with a primary indication of neurological features), telegenetics may be an equally viable, if not better modality as opposed to an in-person evaluation. This would alternatively apply to patients with an indication associated with a lower testing diagnostic yield, whose clinical assessment may be more suitable for an in-person evaluation.

2.5.6 Limitations

A limitation in the collection of data used to conduct this study was that much of the phenotypic data used to determine the primary indication were subjective. To ameliorate some of the subjectivity in determining primary indication, broad groupings were established to aid in interpretation. If the primary referral indication did not match that of the primary testing indication, the primary testing indication was the indication used for this study. This was based on the primary ICD-10 code classification that was decided on by the ordering physician at the time testing was ordered. When patients had multiple indications, the primary indication based on ICD-10 codes was used.

Testing strategy was recorded in the abstraction of data from EMR; however, we did not analyze the differences in strategies between the two populations. Differences in testing strategy may alter the diagnostic yield based on indication for which that testing strategy was implemented. The descriptive information that was collected can be found in Appendix D.

Additionally, this study did not analyze provider differences regarding distribution of in-person and telehealth patients per provider, likelihood of diagnostic outcomes, and differing testing strategies by provider. Provider differences may impact

the interpretation of the results found in this study, if certain providers with altering practice strategies between IP and TH visits have an uneven distribution of the different populations used for this study. This may also be the case with respect to differences made in providers' documentation. Given that the categorical assignments were based on providers' documentation, clinical assessment outcomes may differ significantly even for the same phenotypic indication. This can be most notable in the qualitative differences in which an indication, such as Joint Problems, was assigned differing clinical outcomes despite similar indications. Some providers documented clearly in the EMR for patients being seen to rule out hEDS, that the patient outcome was Within Normal Variation (or did not meet criteria), whereas others instead determined patients to have benign joint hypermobility syndrome, thus their categorization as Clinical Diagnosis. Differences in documentation could therefore affect the differences seen in clinical outcomes based on assessment for patients included in this study.

Finally, time constraints limited the number of patients included in this comparison analysis. Some categories included in our analysis to determine clinical assessment outcomes for comparison had values that were less than five. Due to the small sample size, the external validity of testing may not necessarily be generalizable to that of the general population. Future analysis involving larger sample sizes for comparison would aid in determining if some of the statistically significant differences identified can be replicated in a larger sample size.

CHAPTER 3

CONCLUSION

Given the many benefits for both patients and providers that have been previously studied in using telemedicine for patient care, our research provides further justification for the use and utility of telegenetics as a means to provide genetic services across a broad range of pediatric patients seeking genetic evaluations. Telemedicine continues to be an area of interest across many medical specialties in making healthcare more equitable, available, and accessible. Though much of the research has been surrounding the satisfaction of patients and providers in these alternative delivery services, the literature has been lacking quantifiable data that would suggest similar outcomes for patients receiving telegenetic services when compared to those who have received in-person genetic services. The data generated by our research suggest that the efficacy of pediatric telehealth visits would not differ significantly from that of an in-person genetic evaluation in terms of the overall diagnostic outcomes. Though more studies are needed to determine the differences that can be seen in clinical assessment outcomes, our research provides support that these differences did not affect the diagnostic outcome.

Implementing successful telegenetics programs has largely been constrained by limitations in reimbursement from health insurers when compared to in-person evaluations. The low reimbursement rates have also contributed to limited research in the effectiveness of telehealth programs as it pertains to diagnostic outcomes across specialties, and has been cited in a number of other studies as a limiting factor in the

sustainability of maintaining telegenetics as an option for patients seeking genetic services (Hilgart et al., 2012; Lea et al., 2005; Terry et al., 2019). With the expansion of services covered by CMS during the COVID-19 PHE, telemedicine as a whole has made a considerable footprint in how healthcare providers can provide services to patients. With the previous literature suggesting high satisfaction rates among patients and providers, it is unlikely that this increasingly popular alternative service model will disappear once the PHE is over. This study supports telegenetics as a comparable alternative to in-person evaluations moving forward. Additionally, the differences between the two populations that were highlighted in our results identify areas of needed improvement and future research in order to minimize provider limitations and patient barriers in future provision of telegenetics services

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APPENDIX A

PRIMARY INDICATIONS WITH SUBGROUPS

Neurodevelopmental Disorders	
Developmental Delay	Unspecified
Global Delay	Speech, fine motor, gross motor, cognitive, personal/social (Needs to have delays in 2 or more of domains listed above)
Speech Delay	Unspecified, expressive, receptive, mixed, apraxia, dyspraxia, articulation
Fine Motor Delay	Unspecified
Gross Motor Delay	Unspecified, non-ambulatory
Autism	Diagnosis based on ADOS
Intellectual Disability	IQ <70 or a clinical diagnosis of intellectual disability without available IQ
Learning Disability	ADHD, dyslexia, "slow learner," history of special education without a diagnosis of ID
Regression	Any history of regression in skills
Structural Anomalies	
Brain	Congenital brain anomalies, abnormal MRI, agenesis of corpus callosum, cerebellar dysplasia, enlarged cerebellum, enlarged vermis, small cysts, small peduncles, fused cerebellum, underdevelopment of left frontal lobe, dysgenesis of corpus callosum, hypoplastic septum pellucidum, small corpus callosum, holoprosencephaly, cortical dysplasia, dandy-walker variant, shortened corpus callosum, cerebral ventriculomegaly, polymicrogyria, cerebellar white matter abnormalities, periventricular leukomalacia (MRI in NICU), hemimegalencephaly, interhemispheric brain cyst, cortical dysplasia, thin corpus callosum, brain malformations, small cerebellum, Chiari malformation, hydrocephalus, cerebral ventriculomegaly, cerebellar ectopia, periventricular leukomalacia found shortly after birth, agenesis of corpus callosum, polymicrogyria, midline arachnoid cyst, schizencephaly, periatrial heterotopias, brain stem underdevelopment, changes in cortical sulcation and opercularization patterns, spinocerebellar atrophy, cerebral atrophy, brain tumors, brain hemorrhage, IVH, white matter atrophy, abnormal brain MRI, leukodystrophy, brain cyst, cerebral atrophy, benign external hydrocephalus, hemimegalencephaly, pseudotumor cerebri, delayed myelination, leukomalacia cortical thickening, ectopic posterior pituitary gland, glioma, focal cortical dysplasia, benign enlargement subarachnoid space of infancy
Congenital heart defects (CHD)/Cardiac/vasculature	Patent foramen ovale, ventral septal defect, tricuspid valve defect, mild supravalvular aortic narrowing, atrial septal defect, left sided superior vena cava, congenital heart defect, patent ductus arteriosus, atrioventricular canal defect, coarctation of the aorta, short aortic arch, tetralogy of Fallot, aortic root dilation, left ventricular enlargement, small internal carotid artery, hypoplastic aortic arch, dilated cardiomyopathy, hypertrophic cardiomyopathy, AV malformations, Galen aneurysmal malformations (VGAM), hemangioma (internal), lymphatic malformation, cor triatriatum sinister, single coronary artery, pulmonic valve stenosis
Genitourinary/renal Anomalies	Penile torsion, undescended testes, shawl scrotum, penile chordee, hypoplastic labia, genital anomalies, cryptorchidism, hypospadias, small vaginal area, undescended testicle, small uterus with no connection of cervix to vagina, hypoplastic vagina, ambiguous genitalia, hydronephrosis, small right kidney, underdeveloped kidney, ureteropelvic junction obstruction, hydrocele, thickening of the glomerular basement membrane, adrenal cysts, duplicated collecting system, multicystic kidney
Craniofacial	Submucosal cleft palate, cleft lip +/- cleft palate, bifid uvula, Pierre Robin sequence, cleft lip and palate, pseudocleft of the upper lip, choanal atresia, Microcephaly, macrocephaly, relative microcephaly, turricephalic head, dolichocephaly, trigonocephaly, acquired microcephaly, plagiocephaly, narrow cranium, relative macrocephaly, borderline microcephaly, micrognathia, prominent forehead, frontal bossing, craniosynostosis, macroglossia, delayed fontanelle closure, harlequin deformity of the orbit(s), macroglossia
Eye	Chorioretinal colobomas, ocular anomalies, optic nerve hypoplasia, eye anomalies, optic nerve hypoplasia, hypoplasia of fovea centralis, optic nerve abnormalities, optic nerve atrophy, congenital macular scar, microphthalmia, lacrimal duct abnormality, blepharophimosis
Musculoskeletal	Skeletal dysplasia, abnormal radiographic findings, congenital scoliosis, clinodactyly, joint contractures, club foot/feet, rhizomelia, micromelia, transverse limb defect, polydactyly, clinodactyly, limb reduction defect, bowing of lower legs, positional scoliosis, hip dysplasia,

	pectus carinatum, pectus excavatum, kyphoscoliosis, chondrodysplasia punctata, butterfly vertebra, absent rib, underdeveloped tibias, radial clubbing of hands, scoliosis, vertebral anomalies, low bone density, short neck, wide neck, broad neck, torticollis, branchial cleft, sacral dimple, Short toes, 2-3 toe syndactyly, toe contractures, abnormality of foot, sandal gap toes, webbing of toes, wideness of forefoot, pes planovalgus, broad great toes, brachydactyly, hypoplasia of the toes, small hands, short hands, stub thumbs, single transverse palmar crease, bridge palmar crease, horizontal crease on left hand, square-shaped thumbs, short metacarpal bones, camptodactyly, short metacarpals, short 5th fingers, long thin tapered fingers, brachydactyly, hypoplastic thumbs, single flexion crease on 5th fingers, adducted thumbs, syndactyly, symbrachydactyly, Poland anomaly, scoliosis, kyphosis, knock knees
Gastrointestinal	Anal atresia, TE fistula, Hirschsprung, bilateral hernia, hernia, umbilical hernia, diaphragmatic hernia, inguinal hernia, intestinal malrotation, polysplenia, esophageal atresia, intussusception, polyposis, intestinal perforation, septated subcapsular hepatic lobe cyst
Ear	Low set ears, abnormal cartilage of external ears, preauricular tag, over folded helices, large ears, overfolded helices, mildly cupped ears, low set ears, dysmorphic ears, thick ear helices, misshapen right ear, posteriorly rotated ears, simple helices, left ear abnormality with prominent tragus/extra tissue, abnormally shaped ears, cupped ears, posteriorly rotated ears, small ears, thick helices and antihelices, otosclerosis, earlobe crease
Integumentary: skin	Café au lait, mongolian spots, hypopigmented macules, swirling pigmentation, vitiligo, ash leaf spot, variable pigmentation of the skin, wide spaced nipples, stretchy skin, dermal histiocytosis, irregular capillary vascular malformation of the skin, hemangioma (cutaneous), ichthyosis, nevus flammeus, ichthyosis
Dysmorphic facies	Unspecified dysmorphic features of the face, eyes, ears, nose, lips, facial structure. Or dysmorphic features include two or more dysmorphic features of the face, eyes, ears, nose, lips, facial structure.
Integumentary: hair/nails	Increased hair on back, thick eyebrows, synophrys, abnormal hair pattern and growth, thin hair, low anterior hairline, sparse hair in parietal areas, sparse blonde hair, increased hair on arms, low anterior hairline, synophrys, abnormal eyebrows, nail anomalies, brittle nails, concave nails, deepset nails, fingernail hypoplasia, hyperconvex fingernails, small nails, thin nails
Dental	Tooth anomalies, dental anomalies, dental abnormalities, missing adult tooth, brittle teeth, diastema in central upper incisors, wide spaced teeth, small unusually shaped teeth
Neurological Features	
Neurological- Unspecified	Unspecified, trauma, hypoxic event, nonspecific abnormal EEG (excessive background slowing for age, etc)
Abnormal Movement	jerky upper body movements, spasticity, abnormal twitching and jerking, abnormal movements, dystonia, clonus, spastic quadriplegia, severe dystonia, tremors in hands and feet, benign shuttering attacks, hand tremors, hyperkinesis, choreathetoid movement, spastic diplegia, paroxysmal torticollis
Coordination/Gait/Balance	Unsteady gait, episodic ataxia, abnormal ambulation, coordination impairment, waddling gait, wide based gait, ataxia, poor balance, abnormal gait, ataxia, inability to walk, balance issues, gait abnormality, toe-walking, mild gait imbalance, uncoordinated gait
Seizures	Unspecified, generalized, myoclonic, tonic clonic, focal, absence, infantile spasms
Neuromuscular	Unspecified weakness, neuropathy, myopathy, muscular dystrophy, hyperreflexia, hyporeflexia, increased deep tendon reflexes, absent deep tendon reflexes, muscle wasting, myotonia
Additional Features	
Prematurity/complications of prematurity	Born prior to 37w, apnea of prematurity, anemia of prematurity, intraventricular hemorrhage related to prematurity, retinopathy of prematurity
Gastrointestinal- non-structural	GERD, GI complications, recurrent intestinal obstruction, delayed gastric emptying, eosinophilic esophagitis, chronic diarrhea, gastroparesis, gastrointestinal dysmotility, liver fibrosis, feeding difficulty requiring gtube, bowel obstruction
Joint	joint pain, joint laxity, stiff joints, joint hypermobility, hyperextensibility, progressive stiff joints, multiple dislocations
Behavioral/Psychiatric	Sensory processing issues, behavioral issues, anxiety, self-injurious behaviors, OCD, severe anxiety, head banging, depression, social anxiety, behavioral issues, psychiatric concerns, bipolar disorder, oppositional defiant disorder, under-socialized conduct disorder, aggression, mental health issues, separation anxiety, ASD suspected clinically + failed MCHAT or STAT, Tourette's
Hearing Loss	Hearing loss, auditory neuropathy, sensorineural hearing loss, conductive hearing loss
Pulmonary/Respiratory	Pulmonary problems, chronic lung disease, respiratory distress, congenital hypoventilation syndrome, respiratory distress, asthma, recurrent respiratory infections, respiratory issues, laryngomalacia
Ophthalmologic- non-structural	Vision loss, cortical vision impairment, severe myopia, visual impairment, retinitis pigmentosa, FEVR, chorioretinal scarring, photophobia, pupil dilation abnormalities, problems with tracking, lazy eye, retinal pigmentary changes, corneal abrasions, ectopic lentis, crystalline corneal dystrophy, decreased fundus pigmentation, peripheral iris transillumination defects, blunted foveal reflexes, decreased fundus pigmentation, abnormal eye movements, nystagmus, exotropia, esotropia, strabismus, ptosis

Metabolic Measures	Electrolyte problems, concern for mitochondrial disorder, Low blood glucose, selective IgA deficiency, ketotic hypoglycemia, mildly elevated CK, elevated plasma homocitrulline, elevated lactate, hyperlipidemia, hyperglycemia, hyperphosphatemia (no known bone or renal conditions), mitochondrial abnormalities, vitamin d deficiency, mitochondrial abnormalities, metabolic abnormalities, elevated lactic acid, elevated alkaline phosphatase, mitochondrial dysfunction, rhabdomyolysis, proteinuria, episodes of ketosis
Cardiac- non-structural	Heart murmur, heart-left bundle block, bradycardia, postural orthostatic tachycardia syndrome, LQT, rhythmic abnormality, SVT
Renal/Genitourinary- non-structural	vesicoureteral reflux, chronic kidney disease, hx kidney issues and surgeries, kidney disease, neurogenic bladder, steroid-resistant nephrotic syndrome/FSGS/focal segmental glomerulosclerosis, glomerulary abnormality
Endocrine	Hypothyroidism, thyroid disease, precocious puberty, amenorrhea, hyperparathyroidism, congenital hypothyroidism, PCOS
Hematologic	Anemia, neutropenia, hematologic malignancies, epistaxis, hematemesis, thrombocytopenia
Growth	FTT, obesity, poor weight gain, rapid growth, tall stature, short stature, hemihypertrophy
Other	Indications that do not fall within any of the other categories; multiple tumors (nonmalignant or malignancies)
Suspected/known conditions	
Family history	Known genetic condition, carrier of genetic condition, NDDs
Recognizable genetic condition	Rule out or rule in suspected condition; patient has clinical diagnosis of genetic condition; patient already has molecular diagnosis of a genetic condition, which was obtained by previous testing
Genetic testing completed by an outside provider prior to visit	Patient already has a molecular diagnosis and is being seen to establish care with genetics, patient requires genetic counseling on testing ordered by an outside provider, outside testing results require genetic evaluation to establish clinical relevance

Figure A.1 *Descriptive details found within Primary Indications*

APPENDIX B

CLINICAL ASSESSMENT DESCRIPTIVE DATA

Clinical Diagnosis Based on Exam			
Broad Group	**Indication**	**Number of Patients (n=7)**	**Assessment Details**
Suspected/Known Condition	Recognizable Genetic Condition	3	oculocutaneous albinism, incontinentia pigmenti, cleidocranial dysplasia (CCD)
Additional Features	Joint Problems	3	benign joint hypermobility syndrome
Structural Anomalies	Integumentary: Skin Abnormality	1	NF1
Environmental Etiology			
Broad Group	**Indication**	**Number of Patients (n=15)**	**Assessment Details**
Neurodevelopmental Disorders	Developmental Delay	9	in utero drug exposure, birth trauma, prematurity
Neurodevelopmental Disorders	Gross Motor Delay	1	birth trauma
Structural Anomalies	Brain Anomaly	1	birth trauma, exposures
Structural Anomalies	Craniofacial Anomalies	1	uterine constraint
Additional Features	Prematurity	2	prematurity
Additional Features	Growth Related	1	Prematurity
Multifactorial Etiology			
Broad Group	**Indication**	**Number of Patients (n=4)**	**Assessment Details**
Suspected/Known Condition	Recognizable Genetic Condition	3	r/o HED (dx eczema); r/o FASD (social/env, familial, ADHD)
Neurodevelopmental Disorders	Autism	1	prenatal exposure, complicated social/fhx, parents with mental health
Isolated Feature			
Broad Group	**Indication**	**Number of Patients (n=15)**	**Assessment Details**
Neurodevelopmental Disorders	Developmental Delay	1	isolated macrocephaly due to ventriculomegaly
Structural Anomalies	Brain Anomaly	1	neural tube defect
Structural Anomalies	Structural Heart Anomaly	2	congenital heart defect
Structural Anomalies	Genitourinary/Renal Malformations	1	
Structural Anomalies	Craniofacial Anomalies	6	
Structural Anomalies	Musculoskeletal Anomalies	1	
Structural Anomalies	Gastrointestinal Anomalies	2	polysplenia heterotaxy syndrome, isolated gastroschisis
Suspected/Known Condition	Recognizable Genetic Condition	1	r/o McCune Albright- isolated precocious puberty due to ovarian cysts
Within Normal Variation			
Broad Group	**Indication**	**Number of Patients (n=27)**	**Assessment Details**
Neurodevelopmental Disorders	Developmental Delay	9	
Neurodevelopmental Disorders	Speech Delay	10	
Structural Anomalies	Ear Abnormality	1	
Structural Anomalies	Integumentary: Skin Abnormality	1	
Additional Features	Joint Problems	3	does not meet criteria for hEDS

Suspected/Known Condition	Family History	1	paternal family history X-linked condition; patient female
Suspected/Known Condition	Recognizable Genetic Condition	2	r/o FASD; r/o Marfan

Figure B.1 *Descriptive details regarding clinical assessment based on exam: IP*

Clinical Diagnosis Based on Exam			
Broad Group	**Indication**	**Number of Patients (n=9)**	**Assessment Details**
Structural Anomalies	Musculoskeletal Anomalies	1	Poland anomaly syndrome
Additional Features	Joint Problems	5	benign generalized joint hypermobility
Additional Features	Growth Related	1	growth hormone deficiency
Suspected/Known Condition	Recognizable Genetic Condition	2	r/o hEDS- dx benign joint hypermobility syndrome; NF1
Environmental Etiology			
Broad Group	**Indication**	**Number of Patients (n=9)**	**Assessment Details**
Neurodevelopmental Disorders	Developmental Delay	3	prenatal exposure
Neurodevelopmental Disorders	Global Delay	1	prenatal exposure
Additional Features	Prematurity	2	prematurity
Additional Features	Behavioral/Psychiatric	1	
Additional Features	Growth Related	1	Intrauterine growth restriction (IUGR)
Suspected/Known Condition	Recognizable Genetic Condition	1	r/o fetal alcohol syndrome (FASD)- in utero drug
Multifactorial Etiology			
Broad Group	**Indication**	**Number of Patients (n=8)**	**Assessment Details**
Neurodevelopmental Disorders	Developmental Delay	2	prenatal exposure, abuse, family history
Neurodevelopmental Disorders	Learning Delay/Disability	2	ADHD/behavioral (familial)
Neurodevelopmental Disorders	Autism	1	
Neurodevelopmental Disorders	Speech Delay	1	Family history
Structural Anomalies	Craniofacial Anomalies	1	multifactorial CL+CP and club foot
Structural Anomalies	Musculoskeletal Anomalies	1	mild infantile scoliosis
Isolated Feature			
Broad Group	**Indication**	**Number of Patients (n=3)**	**Assessment Details**
Neurodevelopmental Disorders	Developmental Delay	1	Macrocephaly due to BESSI- likely contributing to delay
Structural Anomalies	Structural Heart Anomaly	2	CHD
Within Normal Variation			
Broad Group	**Indication**	**Number of Patients (n=12)**	**Assessment Details**
Neurodevelopmental Disorders	Developmental Delay	3	
Neurodevelopmental Disorders	Speech Delay	3	
Structural Anomalies	Musculoskeletal Anomalies	1	
Additional Features	Joint Problems	1	no hypermobility present
Suspected/Known Condition	Family History	1	
Suspected/Known Condition	Recognizable Genetic Condition	3	r/o Marfan; did not meet criteria

Figure B.2 *Descriptive details regarding clinical assessment based on exam: TH*

APPENDIX C

CLINICAL AND TESTING OUTCOMES

Clinical Assessment Outcomes	
Clinical Diagnosis Made	NF1, hEDS, OCA, amniotic band syndrome, isolated growth hormone deficiency, generalized joint hypermobility, Poland anomaly syndrome, Incontinentia Pigmenti, cleidocranial dysplasia, hypermobility spectrum disorder
Environmental	Prematurity, in utero drug/alcohol exposures, birth trauma, growth related to IUGR, home environment, abuse/trauma, non-nurturing early home life, neglect
Multifactorial	Behavioral/mental health related issues, eczema, learning disability (ie. dyslexia), postural kyphoscoliosis, ADHD/behavioral (familial), clubfoot and hip dysplasia, speech apraxia, high functioning autism
Within Normal Variation	Speech delay, familial trait, delays but making progress as expected, mild joint hypermobility, within normal variation after adjusting for prematurity, rule out Marfan syndrome
Isolated	CL+/-CP, craniosynostosis, heart defect, limb defect, polysplenia heterotaxy syndrome, neural tube defect, isolated congenital feature or structural anomaly
Testing Not Indicated	Follow up if no developmental progress made, no concern for genetic etiology, too low of a yield to warrant cost of test, testing completed prior to visit from outside/referring provider, patient already has diagnosis, path/LP/VUS found on outside testing consistent with clinical features, patient needs another evaluation prior to testing, "wait and see" approach, initial testing more appropriate in a family member/relative
Testing Indicated	
Testing Outcome	
Diagnostic (Includes diagnostic results with variable expressivity and VUS's felt to be clinically significant)	LP Xp21.3p21.1 duplication; tetrasomy 9p (9p24.3-9p11.2); path 15q13.2q13.3 BP4-B5 loss, LP *SCN8A*; trisomy 21; LP *KDM5C*; path mutation in *EDA*; 7q11.23 duplication syndrome, path 18Mb 4q deletion; LP mutation in *PTEN*; de novo LP variant in *ZMIZ1*; 2 heterozygous path mutations in *GAA*; LP variant in *KDM5C*; path 9.4 Mb loss of 11p15.1p14.1; de novo path *MAGEL2* variant; 2 path variants in *RPGRIP1L*; 18q deletion syndrome; 2 heterozygous mutations in *DHCR7*; path loss at Xp22.31 assoc with XL ichthyosis; LP variant in *CACNA1A* (mat); path *PTPN11* variant; de novo path *SLC6A1* variant; familial path *APC* variant; Familial variant in *COL1A1* (VUS), with clinical dx of OI, 15q11.2 BP1-BP2 loss, path 15q13 BP4-BP5 deletion (mat); pathogenic mutation in *TP63* associated with ectrodactyly ectodermal dysplasia VUS's felt to be clinically significant: *GDF2* (AD HHT type 5); FS de novo mutation in *CCAR1*; VUS in *NF1*; pat inherited *RELN* VUS (dad hx sz) thought to be gene of interest; VUS in *SLC6A8* (hemizygous)
Undiagnosed	Normal result- no variants detected Secondary finding/carrier status: *NDUFB3*, AR mitochondrial complex I deficiency; LP *NRXN1*; 11p15 loss carrier for delta-beta thal; path *HPS1* (hermansky pudlak I); path mutation in *SLC26A4* (pat; assoc with AR condition); carrier of path *GAMT* variant; LP variant in *MSH6*, VUS in *ALDOA* gene (AR GSD XII), loss of homozygosity Partially relevant to features: 3p26.3 491kb gain- includes exon 1 of *CNTN6*; VUS fs mutation in *HCN4* (assoc with arrythmias and LVNC); VUS loss at 1p35.1; 1 path variant in *PDZD7* (pat), 2 VUSs in *PDZD7* (mat) Not felt to be clinically relevant: 7p14.1 238kb gain; 4q32.1 loss; 11p13 gain; 19q11 gain; LB 4q26 gain; 1 VUS in ASPM (assoc with AR condition); VUSs: 11q13.4 (mat), Xp22.33 (pat); VUS gain of 16q24.1; VUS in *MN1* (pat), VUS gain at 4p16.1, VUS gain at 6q26; VUS gain of 12q24.11 and 20q11.21; 2 VUSs: 11q14.3 gain (mat), 18q22.1 gain (pat); 2 VUSs in *CLN6* and *SZT2* (both assoc with AR conditions); 81kb gain at 4q33
Uncertain	*NLGN4X*, maternal; 10q26.3 gain; *RELN* (mat); VUS gain of 17q24.3; VUS: 3p22.2 gain and 7q33 gain; VUS gain of 7q31.1; VUS in *ASH1L*, 2 heterozygous changes in *SKIV2L* (LP and VUS); VUS gain of 2p25.3; 2 VUSs: 9p24.3 and 19q13.41 gains; 2 variants in cis in *CDH23* (pat), 1 variant in *USH2A* (mat); VUS in *TANC2* (pat); VUS 7q21.1 loss; 2 heterozygous VUSs in *ALDH18A1*, 1 VUS in *GJC2*

Not Completed	Sample Not Returned Insurance Related: Pre-authorization issues, pre-authorization denied, no pre-authorization ordered Parents deferred testing: wait and see, cost, okay with just a clinical diagnosis Loss to follow-up: did not return calls/letters for 2nd tier testing Other: provider deferred to test a family member first, provider deferred to wait on records or present to colleagues, there was an issue in ordering the test, sample failure, saliva kit was never sent

Figure C.1 *Descriptive details found in patient clinical assessments and testing*

APPENDIX D

TESTING STRATEGIES

In-Person	Telehealth
Karyotype	-
CMA	CMA
FMR1	-
-	MS-MLPA
Single Gene	Single Gene
NGS Panel	NGS Panel
Focused Panel	Focused Panel
WES	WES
Targeted	Targeted
Karyotype + CMA	Karyotype + CMA
Karyotype + Single gene	-
CMA + FMR1	CMA + FMR1
-	CMA + MS-MLPA
-	CMA + Single gene
CMA + NGS Panel	CMA + NGS Panel
CMA + WES	CMA + WES
-	MS-MLPA + Single gene
Karyotype + CMA + FMR1	Karyotype + CMA + FMR1
Karyotype + CMA + NGS Panel	Karyotype + CMA + NGS Panel
Karyotype + CMA + FMR1 + NGS gene panel	-
CMA + FMR1 + MS-MLPA	
CMA + FMR1 + single gene	CMA + FMR1 + single gene
CMA + FMR1 + WES	CMA + FMR1 + WES
Karyotype + CMA + FMR1 + WES	-
Karyotype + CMA + FMR1 + MS-MLPA + Single gene	-
Karyotype + CMA + FMR1 + MS-MLPA	Karyotype + CMA + FMR1 + MS-MLPA
Karyotype + CMA + FMR1 + single gene	Karyotype + CMA + FMR1 + single gene
Karyotype + CMA + single gene	-

Figure D.1 *Tier 1 testing outcomes for IP and TH patients*

In-Person	Telehealth
CMA	CMA
-	Single Gene
NGS Panel	NGS Panel
Focused Panel	Focused Panel
WES	WES
CMA + WES	-
-	Targeted + Single gene
-	Xon array of single gene + Focused Panel
Xon array of gene panel	Xon array of gene panel

Figure D.2 *Tier 2 testing outcomes for IP and TH patients*