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Analysis of Referrals to Genetics for Suspected Hypermobile Ehlers-Danlos Syndrome

THESIS

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by

Hanae Sugiura

Thesis Committee:

Professor Maureen Bocian, Chair
Adjunct Professor Pamela Flodman
Assistant Clinical Professor Katherine Hall

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DEDICATION

To

my parents, sister, and friends for their tremendous support and unconditional love

"No other disease in the history of modern medicine has been neglected in such a way as Ehlers-Danlos Syndrome."

— Professor Rodney Grahame

"...Until now."

— Victoria Graham

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GLOSSARY

List of abbreviations

Abbreviation	Meaning
cEDS	Classical Ehlers-Danlos syndrome
EDS	Ehlers-Danlos syndromes
G-HSD	Generalized hypermobility spectrum disorder
GI	Gastrointestinal
GJH	Generalized joint hypermobility
hEDS	Hypermobile Ehlers-Danlos syndrome
HSD	Hypermobility spectrum disorder
JH	Joint hypermobility
JHS	Joint hypermobility syndrome
vEDS	Vascular Ehlers-Danlos syndrome

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ABSTRACT OF THE THESIS

Analysis of Referrals to Genetics for Suspected Hypermobile Ehlers-Danlos Syndrome

by

Hanae Sugiura

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Professor Maureen Bocian, Chair

Hypermobile Ehlers-Danlos Syndrome (hEDS) is a condition with heterogeneous clinical features characteristic of a connective tissue disorder (CTD) including generalized joint hypermobility, hyperextensible skin, joint subluxations/dislocations and commonly associated comorbidities such as postural orthostatic tachycardia syndrome and fatigue (Castori et al., 2017; Gensemer et al., 2021). hEDS is the only one among 13 Ehlers-Danlos syndrome (EDS) subtypes without a known etiology or targeted clinical molecular genetic testing, requiring strict clinical diagnostic guidelines and exclusion of other similar conditions (Malfait et al., 2017). Possibly due to the diverse clinical symptoms and the lack of molecular confirmation, hEDS referrals for evaluation for hEDS may be increasingly inundating and overwhelming genetics clinics. This study was a retrospective chart review that analyzed 143 referrals for suspected hEDS/CTD to the University of California, Irvine (UCI) adult genetics clinic and the referring providers' relevant medical notes, if available. The purpose of this research was to understand why medical professionals refer patients with suspected hEDS/CTD for genetic evaluation and what they document in the referral. First, a classification scheme to identify appropriate referrals

was developed using a consensus process. Utilizing a system with four categories of appropriateness, 51% (N=74) of referrals were found to lack enough details to be categorized as appropriate. Additionally, features recorded in the referral documentation were analyzed, and many features related to CTD aside from joint involvements either had not been assessed or were not documented. Many referrals (>75%) also did not document the presence or absence of certain CTD-related features including dislocations, subluxations, easy bruising, and elastic skin. Furthermore, the classification of appropriateness for the primary care referrals differed significantly from that for the referrals from specialist providers ($\chi 2$ (3) = 10.48, p=0.02). Referrals from primary care providers were more likely to be missing details (N=26, 47% compared to N=19, 22% for specialty referrals). The findings suggest that educational outreach to referring providers and implementing a referral protocol may help improve the quality of referrals and, ultimately, for genetics clinics to be able to provide optimal support to patients suspected with hEDS/CTD and the providers involved in their medical journeys.

INTRODUCTION

I. Connective tissue disorders

Connective tissues provide essential structural support for the body, binding together its cells, organs, and tissues (Murphy-Ryan et al., 2010). Not surprisingly, there are over 200 different types of acquired and hereditary connective tissue disorders (CTD) (NIH, 2016). While both genetic and environmental factors can affect susceptibility to develop acquired CTD such as lupus, hereditary CTD are caused primarily by genetic variants in genes that code for components of connective tissues like collagen and elastin (Murphy-Ryan et al., 2010). Harmful variations in these genes result in improper development of connective tissue components and insufficient structural support (Castori et al., 2017; Murphy-Ryan et al., 2010). While some hereditary CTD like Marfan Syndrome and Osteogenesis Imperfecta have known etiological variations in one or more single genes, some do not (Colombi et al., 2015; Malfait et al., 2017). Conditions without confirmatory testing require a clinical diagnosis. Also, clinical manifestations of some CTD are broad and typically overlap, possibly resulting in misdiagnosis (Colombi et al., 2015; Murphy-Ryan et al., 2010). One such disorder is hypermobile Ehlers-Danlos syndrome (hEDS), a subtype of the Ehlers-Danlos syndromes.

II. History of hypermobile Ehlers-Danlos syndrome (hEDS)

Ehlers-Danlos syndrome (EDS) is a group of heritable CTD whose cardinal features include joint hypermobility (JH), skin hyperextensibility, and tissue fragility (Malfait et al., 2017). Subtyping EDS has been a complex and difficult process due to the heterogeneous clinical symptoms. Because of this challenge, EDS has continued to be reclassified ever since its recognition. The current EDS classification is related to their different genetic etiologies. There

are 13 subtypes, of which 12 have known genes. Only hEDS does not have a known genetic etiology (Malfait et al., 2017).

In the beginning of the 1900s, two dermatologists Edward Ehlers and Henri-Alexandre Danlos each presented a case with JH and/or skin abnormalities such as hyperextensibility and abnormal skin lesions (Hamonet et al., 2015; Parapia & Jackson, 2008). The condition was formally suggested to be named after them in the 1930s (Gensemer et al., 2021; Hamonet et al., 2015; Parapia & Jackson, 2008). Since then, determining the clinical description of EDS and deciding on the inclusion and exclusion of clinical features has been a topic of discussion (Hamonet et al., 2015; Parapia & Jackson, 2008). EDS reclassification began in the late 1960s when the syndrome was thought to have five clinically distinguishable groups (Beighton, 1970). In 1988, the 1986 Berlin Nosology formalized the nomenclature and outlined 11 subtypes labeled with Roman numerals based on clinical manifestations and inheritance patterns (Beighton et al., 1988). For EDS diagnosis, the nosology suggested the exclusion of "cutis laxa" and "familial joint hypermobility syndrome." This is also when hEDS was introduced as EDS type III and was recognized to have autosomal dominant inheritance with clinical symptoms of marked JH, moderately hyperextensible skin, and minimal scarring (Beighton et al., 1988).

As molecular studies advanced, the 1998 Villefranche Nosology revised the classification to six types with defined major and minor clinical criteria and, for some, discovered molecular basis (Beighton et al., 1998). Furthermore, the naming was revamped to be the description of each subtype. EDS type III was renamed as hypermobility type, and it consisted of major diagnostic criteria of skin involvement such as hyperextensibility and/or smooth, velvety skin and generalized hypermobility. The minor diagnostic criteria consisted of recurring joint dislocations, chronic joint or limb pains, and positive family history. The Villefranche Nosology

commented on the importance of distinguishing those with generalized joint hypermobility (GJH) due to rheumatological conditions from individuals affected with hEDS (Beighton et al., 1998).

EDS is currently classified into 13 subtypes under the revised International EDS Classification proposed by The International EDS Consortium in March 2017. The revised classification lists major and minor criteria for each of these subtypes as well as a causative variant (or variants) in all except for hypermobile Ehlers-Danlos syndrome (hEDS) (Malfait et al., 2017). An improved diagnostic guideline for hEDS is expected as the study of hEDS and JH continues to advance. This will help improve the accuracy of research on hEDS, for example, determining the true prevalence of hEDS. hEDS is the most common of the EDS subtypes, followed by classical and vascular EDS (cEDS and vEDS, respectively). The overall prevalence of EDS has been estimated to be 1 in 5,000 (Pyeritz, 2000). Some studies have reported hEDS to have a prevalence of 1 in 3,400 to 3,450 (Brooks et al., 2021; Demmler et al., 2019). The accuracy of these statistics will improve as hEDS continues to be better defined.

III. Current Clinical Diagnostic Criteria for hEDS

The 2017 International Classification of the Ehlers-Danlos Syndromes proposes three criteria for a clinical diagnosis of hEDS. Only when all criteria are met can a diagnosis of hEDS be given.

The first criterion is GJH. GJH is assessed by using the 9-point Beighton scoring system (Malfait et al., 2017). Because the joint range of motion decreases with age, the cut-off score for JH in hEDS varies based on the age group: ≥6 for pre-pubertal children, ≥5 for pubertal adults that are 50 years of age or younger, and ≥4 for those older than age 50 (Hwang & Jung, 2015;

Malfait et al., 2017; Soucie et al., 2011). For adults, with acquired joint limitations such as past surgery and amputations that affect the Beighton score calculation, GJH may be assessed using a 5-point questionnaire (5PQ) (Hakim and Grahame, 2003; Malfait et al., 2017). This has not been validated in children (Malfait et al., 2017). For a Beighton score that is 1 point below the age-specific cut-off, the 5PQ has to have at least two positive items to make a diagnosis of GJH.

Criterion two lists three groups of features, where criteria for two or more groups have to be met (Malfait et al., 2017). One group, or Feature A, catalogs 12 systemic manifestations of a generalized CTD, where having five features is the threshold to fulfill this group. Four of the 12 features account for skin manifestations such as unusually soft or velvety skin, mild skin hyperextensibility, unexplained striae, and atrophic scarring. Individuals with hEDS may also experience recurrent abdominal hernias and pelvic floor, rectal, and/or uterine prolapse. Marfanoid habitus such as arachnodactyly, arm span-to-height ratio of $\geq$1.05, dental crowding, and high or narrow palate may also be present. Echocardiogram is recommended for individuals suspected of hEDS due to the possibility of mitral valve prolapse and aortic root dilation (Malfait et al., 2017).

Feature B in criterion two requires positive family history of one or more first-degree relatives who independently meet the current diagnostic criteria for hEDS (Malfait et al., 2017). Lastly, Feature C requires one of three musculoskeletal complications: (1) musculoskeletal pain, (2) chronic, widespread pain, and/or (3) recurrent joint dislocations (Malfait et al., 2017).

The last criterion notes three requirements that must be met (Malfait et al., 2017). First is that the unusual skin fragility must be absent; if present, other types of EDS should be considered. The second condition is that other heritable and acquired connective tissue disorders such as lupus and rheumatoid arthritis must be excluded. Lastly, alternative explanations or

diagnoses for hypermobility must be excluded. For example, differential diagnoses such as neuromuscular disorders, other hereditary CTD such as other EDS subtypes, and skeletal dysplasias must be assessed and eliminated (Malfait et al., 2017).

IV. Joint hypermobility (JH) / Hypermobility spectrum disorders (HSD)

The difficulty of having joint hypermobility (JH) as one of the major clinical characteristics of hEDS is the wide spectrum, ranging from localized joint hypermobility (LJH), peripheral joint hypermobility (PJH), to GJH. JH in LJH and PJH are more confined; in LJH, the hypermobility is limited to single joints or specific body parts, and PJH typically involves only the joints in hands and/or feet (Castori et al., 2017). On the other hand, JH is usually found in five or more sites with GJH. GJH is seen not only in hEDS but also in other syndromic diagnoses or may also be an isolated diagnostic finding. The clinical spectrum can range from asymptomatic JH that is not clinically significant, through non-syndromic hypermobility with secondary manifestations, to hEDS. In all cases, the Beighton score has to be positive, which would differentiate GJH from other JH such as LJH and PJH. Contrastingly, asymptomatic GJH does not have musculoskeletal involvement such as chronic pain and scoliosis, while generalized hypermobility spectrum disorders (G-HSD) do. Musculoskeletal involvement is also possible in hEDS, challenging diagnostic accuracy due to the possibility of lying anywhere on the spectrum between asymptomatic GJH and G-HSD (Castori et al., 2017).

JH itself is also multifactorial. Genetic variation is thought to have influence on JH (Hakim et al., 2004). What makes the phenotype more complicated, however, is the non-genetic factors; JH can be affected by age, sex, ethnicity, exercise, and other factors (Singh et al, 2017, Tinkle et al., 2017). For example, children tend to have greater joint mobility than adults (Singh

et al., 2017). Additionally, females on average have joints that are more flexible than males, and females develop greater generalized joint laxity after puberty (Castori et al., 2010; Quatman et al., 2008; Remvig et al., 2007). Non-Caucasians are suggested to have significantly higher Beighton scores than Caucasians (Remvig et al., 2007; Singh et al., 2017). With many factors contributing to JH, the process of diagnosis is further complicated. The complex diagnostic process may result in misdiagnosis of hEDS, which can also jeopardize research outcomes.

V. Conditions commonly associated with hEDS

hEDS is often seen along with other features that are not included in the current diagnostic guideline. In addition, there are comorbidities that are commonly associated with hEDS and contribute to the heterogeneity and variable severity of the condition. Some but not all frequently seen symptoms are described below.

Easy bruising may occur in individuals with hEDS. However, it is not profound as seen in other types of EDS, nor is it well-defined (Castori, 2012; Gensemer et al., 2021; Gharbiya et al., 2012; Malfait et al., 2017; Tinkle et al., 2017).

Ocular findings are reported to be associated with hEDS. Affected individuals may have xerophthalmia (dry eyes), increased curvature of the corneas (though not as severe as keratoconus), high myopia, vitreous abnormalities, and minor lens opacities (Gharbiya et al., 2012). However, ocular manifestations are also common in other CTD (Bravo & Wolff, 2006; Jen & Nallasamy, 2016; Gharbiya et al., 2012; Gensemer et al., 2021). Depending on the type of ocular findings, other conditions should be considered first before hEDS. For example, ectopia lentis raises suspicion for Marfan syndrome (Judge & Dietz, 2005).

Gynecologic complications described in the clinical criteria are pelvic floor and uterine prolapse (Malfait et al., 2017). Women with hEDS may also experience menstrual complications such as menorrhagia (heavy menstrual bleeding) (Castori et al., 2012; Tinkle et al., 2017; Gilliam et al., 2020).

Gastrointestinal (GI) manifestations are also seen in many individuals with hEDS. Included in the clinical criteria of hEDS is rectal prolapse (Castori et al., 2015; Malfait et al., 2017; Tinkle et al., 2017). In addition, both structural and functional anomalies are possible. Examples of GI structural anomalies are abdominal and diaphragmatic hernias, internal organ prolapse, and intestinal intussusception (Castori et al., 2015). Reported GI functional anomalies associated with hEDS are gastroesophageal reflux, indigestion, nausea, stomachache, diarrhea, and constipation (Hakim & Grahame, 2004; Zarate et al., 2010; Zeitoun et al., 2013; Castori et al., 2015; Fikree et al., 2017; Tinkle et al., 2017; DiFrancisco-Donoghue et al., 2022). Individuals with hEDS may also experience bloating and reflux symptoms such as heartburn and regurgitation (Zarate et al., 2010; Zeitoun et al., 2013; Tinkle et al., 2017; DiFrancisco-Donoghue et al., 2022).

Autonomic dysfunction, or dysautonomia, is commonly associated with hEDS. Along with the gastrointestinal symptoms listed above, many individuals with hEDS experience orthostatic symptoms, including but not limited to dizziness or light-headedness, fainting, sweating dysfunction, visual disturbances, brain fog, chest pain, shortness of breath, and palpitations (De Wandele et al., 2014, Hakim et al., 2017). The orthostatic symptoms may lead to postural tachycardia syndrome (POTS), neurally mediated hypotension (NMH), orthostatic hypotension, or orthostatic intolerance (Hakim et al., 2017). POTS, orthostatic hypotension, and other forms of orthostatic intolerance were found in 78% of 27 patients with joint hypermobility

syndrome (JHS; Gazit et al., 2003). Similarly, in a study of 144 patients with hEDS or HSD, 70% of the patients were clinically labeled with dysautonomia (Ruiz Maya et al., 2021).

Various mechanisms have been hypothesized to be the cause of autonomic dysfunction in hEDS. According to Hakim et al. (2017), the suggested mechanisms range from low blood pressure to the rare occurrence of brainstem/cervical cord impingement due to Chiari malformation. An excess level of histamine is also a potential cause, supported by animal studies that found histamine to induce hypotension and tachycardia (Hakim et al., 2017; Woods et al., 1977, Skovgaard et al., 2009). Mast cell activation syndrome (MCAS), another condition commonly associated with hEDS, causes a release of excessive histamine (Cheung & Vadas, 2015; Seneviratne et al., 2017; Kohn & Chang, 2020; Frieri et al., 2013; Hakim et al., 2017). MCAS can be seen with POTS as a comorbid condition in the general population as well as in individuals with hEDS (Shibao et al., 2005, Frieri et al., 2013; Cheung & Vadas, 2015, Seneviratne et al., 2017).

A rare but possible cause of autonomic dysfunction associated with hEDS is Chiari malformation (Milhorat et al., 2007, Hakim et al., 2017). A study that included 2813 individuals with Chiari malformation type I found that there were 357 individuals (12.7%) who met the diagnostic criteria for EDS (hypermobile, classic, and arthrochalasia) and related hereditary CTD such as Marfan syndrome, where the diagnosis was established based on the Beighton score, clinical examination, family history, and supplementary tests ranging from echocardiogram to skin biopsy for analysis of collagen (Milhorat et al., 2007). A greater proportion of individuals who had both diagnoses of CTD and Chiari malformation type I experienced symptoms related to the lower brain stem (e.g., nausea, dysphagia, sleep apnea, POTS, and orthostatic hypotension) compared to those who only had Chiari malformation type I (Milhorat et al., 2007).

Some of the participants also had minor neuroradiologic features of occipitoatlantoaxial instability (Milhorat et al., 2007).

However, the causal relationship between hEDS and dysautonomia along with POTS, MCAS, and Chiari Malformation is yet to be determined. To further complicate the situation, while these symptoms may be seen in patients with hEDS as comorbidities, many conditions described are also common in the general population. For example, the prevalence of POTS is about 0.2% in the general population, and the prevalence of MCAS ranges from 0.01% for mastocytosis and monoclonal mast cell activation syndrome to 30% for atopic disorders, depending on the disease spectrum (Sheldon et al., 2015; Akin, 2017). In most cases, hEDS should be low on the differential for these conditions unless they are seen with GJH. Similarly, with certain findings it may be more appropriate to rule out other conditions first before assessing for hEDS, which is a diagnosis of exclusion. In addition, there is variable expressivity of autonomic symptoms among hEDS cohorts, which suggests different etiologies (Martinez et al., 2021). Before assuming that hEDS is the root cause of the autonomic symptoms, it is recommended to consider other possible underlying reasons such as "medications and supplements, cardiac valvular diseases, venous pooling, allergy, autoimmunity, or rarely Chiari malformation" (Hakim et al., 2017).

Lastly, there are nonspecific features that individuals with hypermobility, including those with hEDS, may experience, such as headaches or migraines, anxiety and depression, fatigue, bodily pain, and poor sleep (Hakim & Grahame, 2004, Tinkle et al., 2017, Gensemer et al., 2021, Martinez et al., 2021). According to Martinez et al. (2021), both hEDS and HSD participants experienced generalized pain and self-reported symptoms such as fear of movement, fatigue, and

daytime sleepiness. Many individuals with hEDS may also be diagnosed with chronic fatigue syndrome (Castori et al., 2011).

Regardless of the cause of the conditions mentioned above, ranging from nonspecific indications such as pain to gastrointestinal manifestation and autonomic dysfunction, they contribute to lower quality of life. Health-related quality of life is lower in individuals with hypermobility than in unaffected individuals (Rombaut et al., 2010, Tinkle et al., 2017, Martinez et al., 2021).

VI. Genetics of hEDS

All of the EDS subtypes except hEDS have well-described genetic bases. Many of the genes responsible for the other types of EDS encode for a type of collagen or play important roles in collagen biosynthesis (Malfait et al., 2017; Gensemer et al., 2021). Some EDS subtypes involve defects in other components of the extracellular matrix, such as glycosaminoglycans and procollagen I N-proteinase (Malfait et al., 2017; Gensemer et al., 2021).

The genetic etiology of hEDS is also a topic of interest among researchers. hEDS is observed to be inherited in an autosomal dominant pattern (Malfait et al., 2017; Tinkle et al., 2017). Aside from this, the specific genetic etiology of hEDS remains unknown.

One of the candidate genes for hEDS is *LZTS1*. *LZTS1* encodes a tumor suppressor protein and plays a role in various types of cancer, such as ovarian cancer, hepatocellular carcinoma, and breast cancer (Califano et al., 2010; He & Liu, 2015; Wang et al., 2015). The *LZTS1* gene was brought to light in the context of hEDS when a missense variant was found through a genome-wide linkage study of a three-generation family with hEDS (Syx et al., 2015). Affected family members experienced symptoms such as GJH, musculoskeletal problems, soft

skin, mild atrophic scarring, and easy bruising. Three additional variants in *LZTS1* were found in a subsequent analysis of 230 patients with hEDS or benign JHS (Syx et al., 2015). It is important to note that the study was done before the 2017 International Classification of the Ehlers–Danlos Syndromes criteria were present. However, there have not been any additional studies that further support or refute a causative relationship between *LZTS1* and hEDS.

Collagen genes with variants that are the molecular causes of the other EDS subtypes as well as the gene families are also suspected to have variants that cause hEDS. For example, the *COL5A3* gene, a family gene of *COL5A1* and *COL5A2* genes of which mutations cause cEDS, was denied to be a candidate gene for hEDS in a cohort of 13 individuals with hEDS (Hoffman et al., 2008). Other candidate collagen genes have conflicting findings. Variants in *COL1A1* are described in arthrochalasia and rarely in vEDS and cEDS (Malfait et al., 2017). A segregation study excluded mutations in *COL1A1* gene responsible for a family's JHS but unable to clearly exclude it in another family, requiring additional studies to confirm the findings (Henney et al., 1992). *COL3A1* gene codes type III collagen and its pathogenic variants are the major cause of vEDS (Malfait et al., 2017). A segregation analysis of two families with an autosomal dominant pattern of JHS did not find that *COL3A1* mutations are associated with JHS (Henney et al., 1992). On the contrary, *COL3A1* variant p.G637S was discovered in a family with GJH and minor skin extensibility with softness but without scarring (Narcisi et al., 1994). The family members were diagnosed with EDS III using the diagnostic criteria at that time (the Berlin Nosology) due to the lack of family history of vascular fragility and other clinical signs associated with vEDS, such as thin skin and characteristic facial features (Narcisi et al., 1994). In a more recent study, variants of uncertain significance (VUSs) were found in patients with initial diagnoses of hEDS or benign JHS (Weerakkody et al., 2016). *COL3A1* is illustrative of what is

seen in other collagen genes such as *COL1A1*, *COL5A1*, and *COL5A2* (Henney et al., 1992; Weerakkody et al., 2016).

The *TNXB* gene has also been of interest in investigating the molecular cause of hEDS. Biallelic mutations of *TNXB* confirm the diagnosis of classical-like EDS (Malfait et al., 2017). *TNXB* encodes tenascin XB, an extracellular matrix glycoprotein in the tenascin family (Kaufman & Butler, 2016). Tenascin XB plays a role in collagen organization. In a study by Zweers et al (2003), *TNXB* was associated with hEDS when nine of 14 females with haploinsufficiency ("the situation that occurs when one copy of a gene is inactivated or deleted and the remaining functional copy of the gene is not adequate to produce the needed gene product to preserve normal function" (NCI, 2012)) for this gene met the clinical criteria for hEDS and BJHS used at that time, while none of the 6 males with haploinsufficiency did. Patients with reduced tenascin (TNX) levels experienced hypermobile joints, often with musculoskeletal involvement such as pain. In the study cohort, *TNXB* haploinsufficiency was not seen with skin hyperextensibility and easy bruising, which are clinical features of individuals with TNX deficiency. Lastly, *TNXB* haploinsufficiency was expected to have autosomal dominant inheritance as seen in hEDS and BJHS (Zweers et al., 2003). In another study, three out of 16 hEDS patients with normal TNX serum levels were identified with missense mutations in the *TNX* gene (Zweers et al., 2005). One mutation, Leu4033Ile, was considered non-deleterious because of being described in the SNP database and for unaltered elastic fiber length in the skin of the patient with the mutation; the mutations in the other two patients were thought to possibly be disease-causing. Arg29Trp was hypothesized to be harmful due to arginine residues accounting for almost 15% of the disease mutations (Zweers et al., 2003, Vitkup et al.,

2003). Val1195Met altered the elastic fiber length of the patient significantly (Zweers et al., 2003).

TNXB haploinsufficiency introduced the question of whether some patients with congenital adrenal hyperplasia (CAH) also have hEDS. The most common cause of CAH is the absence of the enzyme 21-hydroxylase, which is due to harmful mutations in the *CYP21A2* gene (Dreves et al., 2023). On chromosome 6, *CYP21A2* lies in between *TNXB* and *TNXA* gene, a highly homologous pseudogene to *TNXB* (Dreves et al., 2023). The 3' end of the *CYP21A2* overlaps the *TNXB* gene (Morel et al., 1989; Miller & Merke, 2018). Due to unequal crossover during meiosis, a large gene deletion can occur, deleting the *CYP21A2* and generating a *TNXA*/*TNXB* chimera (Finkielstain et al., 2011; Lao et al., 2021). Because this contiguous gene deletion syndrome results in *TNXB* haploinsufficiency, some researchers associate CAH with hEDS. In a study of 192 CAH patients with various genotypes, 12 out of 13 CAH patients with *TNXB* haploinsufficiency had EDS clinical features such as JH with chronic joint pain and multiple joint dislocations (Merke et al., 2013). However, some probands also had structural cardiac valve abnormalities such as quadricuspid aortic valve, which is not commonly seen in hEDS (Merke et al., 2013; Malfait et al., 2017; Paige et al., 2020). In a similar study, 10 individuals from seven families had a phenotype of CAH with *TNXA/TNXB* chimeras and were found to have c.12174C>G (p.C4058W), a novel *TNXB* missense variant (Morissette et al., 2015). All 10 CAH patients had clinical features of hEDS such as JH and chronic pain. From other families, three CAH patients were found to have a *TNXB* c.12463+2T>C variant that alters the splice-donor acceptor site. All three had clinical characteristics of hEDS such as JH and dislocations and easy bruising. Decrease in TNX expression was hypothesized to be associated with the hEDS features found in the three individuals (Lao et al., 2021).

New candidate genes continue to be added to the list as analytical and genomic technologies advance. In a recent study, whole-exome sequencing was done on five patients, two of whom are from the same family, with clinical diagnoses of G-HSD (Alanis-Funes et al., 2022). All five patients were found to have mutations in *MUC3A*, *RHBG,* and *ZNF717*. With the advancement of analytic methods, mutations such as these would eventually lead to a better understanding of their health implications.

The challenge and main concern for genetic research on hEDS is whether the participants are correctly diagnosed with hEDS. Misdiagnosis of hEDS is common because of the overlapping phenotype with other CTD, complicated by the difficulty of properly diagnosing individuals with hEDS due to the broad phenotypic spectrum of hEDS and comorbidities. With the possibility of the research participants not truly having the condition (and vice versa - undiagnosed individuals who may truly have hEDS but have not participated in studies), the study results may be jeopardized. However, despite the challenges, exploring a specific genetic etiology of hEDS will most likely continue to be an active area of research.

VII. Other Ehlers-Danlos syndrome subtypes

One of the important steps in the diagnostic process of hEDS is to rule out other CTD, including the other subtypes of EDS. While all the other subtypes can be confirmed through molecular tests, there are individuals with EDS in whom no pathogenic variants are identified in any of the known EDS-associated genes. It would be beneficial to recognize the features that overlap with hEDS and identify the key features that are unique to each of the subtypes. Having specific defining features of each subtype would help in triaging patients referred for possible EDS so that they could be scheduled for evaluation more efficiently.

Classical EDS (cEDS) has major and minor diagnostic criteria. (As defined in the 2017 International Classification of the Ehlers–Danlos Syndromes, a major criterion has high diagnostic specificity because it is present in the vast majority of affected individuals and/or it is characteristic for the disorder and allows differentiation from other EDS subtypes and/or other hereditary CTD. A minor criterion is a sign of lesser diagnostic specificity, but its presence supports the diagnosis (Malfait et al., 2017).) Included in the major criteria are skin hyperextensibility, atrophic scarring, and GJH (Malfait et al., 2017). Minor criteria include easy bruising, soft, doughy skin, skin fragility, hernia, complications of JH (e.g., sprains, luxation/subluxation, pain, flexible flatfoot), family history of a first degree relative who meets clinical criteria, and several other features. Some of these features overlap with hEDS, but most of the phenotypic features are more striking and more severe in individuals with cEDS than in those with hEDS. For example, atrophic scarring in cEDS is more remarkable and prominent (Malfait et al., 2017). Key features may also point to cEDS. High skin hyperextensibility in the presence of molluscoid pseudotumors or widened papyraceous scars should make cEDS higher on differentials (Colombi et al., 2015). cEDS diagnosis is made by a molecular test showing a heterozygous pathogenic variant in one of the genes that encode type V collagen (COL5A1, COL5A2) or rarely in type I collagen (COL1A1; Malfait et al., 2017).

The clinical features of TNXB-related classical-like Ehlers-Danlos syndrome (clEDS) are quite similar to those seen in cEDS, including GJH, hyperextensible skin, and easy bruising. Unlike cEDS, there is no atrophic scarring, inheritance is autosomal recessive, and there are several other features in relatively small percentages of affected individuals that are not found in cEDS, such as thinning and wrinkling of the skin of the hands, anomalies of the fingers and toes, edema of the legs, atrophy of the hand and foot muscles, mild muscle weakness of the

extremities, and several others. Minimal criteria suggestive for clEDS include all three major criteria and a family history compatible with autosomal recessive transmission. However, the diagnosis of clEDS can only be confirmed by finding biallelic TNXB mutations (Malfait et al., 2017).

The rest of the EDS subtypes may be more distinguishable from hEDS by having major features unique to each subtype. Cardiac-valvular EDS (cvEDS) has some similarities to hEDS, cEDS, and clEDS such as JH that is either generalized or only in the small joints, skin hyperextensibility, atrophic scars, thin skin, and easy bruising (Malfait et al., 2017). What makes cvEDS distinctly different from these disorders is the severe, progressive cardiac-valvular problems in the aortic or mitral valves. Unlike cEDS and hEDS, cvEDS is inherited in an autosomal recessive manner. Molecular confirmation is made by finding biallelic pathogenic variants in the *COL1A2* gene (Malfait et al., 2017).

Vascular EDS (vEDS) is one of the most unique EDS subtypes. Major criteria of this autosomal dominant disorder include a family history of vEDS with a documented causative variant in *COL3A1*, arterial rupture at a young age, spontaneous sigmoid colon perforation in the absence of known diverticular disease or other bowel pathology, uterine rupture during the third trimester of pregnancy in the absence of a previous Cesarean section and/or severe peripartum perineal tears, and carotid-cavernous sinus fistula formation in the absence of trauma (Malfait et al., 2017). There are also several minor criteria including some unique ones, such as a characteristic facial appearance, acrogeria (a prematurely aged appearance of the hands), tendon and muscle rupture, and several others. Minimal criteria suggestive for vEDS include family history of the disorder, arterial rupture or dissection in individuals less than 40 years of age, unexplained sigmoid colon rupture, or spontaneous pneumothorax in the presence of other

features consistent with vEDS, any of which should lead to molecular testing for vEDS. Testing for vEDS should also be considered in the presence of a combination of the "minor" clinical features. The diagnosis of vEDS is usually made by identifying a causative variant in one allele of the *COL3A1* gene, which encodes type III collagen, and rarely by finding specific heterozygous arginine-to-cysteine substitution mutations in *COL1A1* (Malfait et al., 2017).

The following EDS subtypes are much less common than those described above. Arthrochalasia EDS (aEDS) most likely will not be in the differential for patients suspected to have hEDS. Individuals with a clinical diagnosis of aEDS should have congenital bilateral hip dislocation, either severe GJH with multiple dislocations/subluxations or skin hyperextensibility, and at least two of the minor criteria, such as kyphoscoliosis, muscle hypotonia, tissue fragility, or several others (Malfait et al., 2017). They could also have muscle hypotonia, kyphoscoliosis, and radiologically mild osteopenia as minor criteria. Heterozygous pathogenic mutations in either *COL1A1* or *COL1A2* that cause entire or partial loss of exon 6 of the respective gene confirm the diagnosis of aEDS (Malfait et al., 2017).

Dermatosparaxis EDS (dEDS) also has striking features that are unique to the subtype. Minimal criteria suggestive for dEDS include major criteria of extreme skin fragility and characteristic craniofacial features plus either one other major criterion (redundant, almost lax skin with excessive skin folds at the wrists and ankles, increased palmar wrinkling, severe bruisability with a risk of subcutaneous hematomas and hemorrhage, umbilical hernia, postnatal growth retardation, short limbs, hands and feet, or perinatal complications due to connective tissue fragility) and/or three minor criteria, such as soft and doughy skin texture, skin hyperextensibility, atrophic scars, GJH, or several others (Malfait et al., 2017). While some of the minor features overlap with cEDS, hEDS, and others, the major features should clearly

distinguish dEDS from the others. dEDS is an autosomal recessive condition due to biallelic mutations in *ADAMTS2* (Malfait et al., 2017).

Minimal criteria suggestive of kyphoscoliotic EDS (kEDS) include congenital muscle hypotonia and congenital or early-onset kyphoscoliosis plus either GJH and/or three minor criteria, some of which apply to the disorder in general and others that are associated with only one or the other of the two involved genes, *PLOD1* and *FKBP14* (Malfait et al., 2017). It is one of the three subtypes that can have blue sclerae and one of the hereditary CTD that can have features suggestive of Marfan syndrome, such as a marfanoid habitus, pectus deformity, and myopia. kEDS is an autosomal recessive condition with biallelic mutations in either *PLOD1* or *FKBP14* (Malfait et al., 2017).

Brittle cornea syndrome (BCS) mainly involves the eyes. Biallelic *ZNF469* or *PRDM5* mutations can cause thin cornea, early onset progressive keratoconus or keratoglobus, and blue sclerae, which are all major criteria (Malfait et al., 2017). Minor criteria encompass other ophthalmological conditions such as corneal scarring, high myopia, and retinal detachment, as well as non-ocular related features such as deafness, developmental hip dysplasia, scoliosis, and arachnodactyly. The brittle cornea syndrome is quite different from the other EDS subtypes and does not seem to resemble EDS at all. However, since several patients with this disorder are clinically suspected to have a form of EDS, the authors of the 2017 International Classification of the Ehlers–Danlos Syndromes believe that its inclusion in the EDS classification is justified (Malfait et al., 2017).

Spondylodysplastic EDS (spEDS) is also an autosomal recessive condition caused by variants in the *B4GALT7*, *B3GALT6*, or *SLC39A13* genes (Malfait et al., 2017). Minimal criteria suggestive for spEDS include short stature and muscle hypotonia plus characteristic radiographic

abnormalities and at least three others of a large number of distinctive minor criteria that are either general or gene-specific (Malfait et al., 2017).

The minimal criteria suggestive of musculocontractural EDS (mcEDS) are age-dependent. At birth or in early childhood, they include congenital multiple contractures and characteristic craniofacial features that are evident at birth or in early infancy, whereas in adolescence and in adulthood they include congenital multiple contractures and characteristic cutaneous features, including skin hyperextensibility, easy bruisability, skin fragility with atrophic scars, and increased palmar wrinkling (Malfait et al., 2017). In spite of the characteristic joint contractures, recurrent/chronic dislocations are included among the 15 minor features. Molecular analysis showing biallelic *CHST14* or *DSE* mutations confirm the diagnosis (Malfait et al., 2017).

Myopathic EDS (mEDS) is currently the only EDS subtype that can be inherited in either autosomal dominant or recessive forms (Malfait et al., 2017). mEDS is caused by heterozygous or biallelic mutations in *COL12A1*, encoding type XII collagen. Minimal clinical criteria suggestive of mEDS include congenital muscle hypotonia and/or muscle atrophy that improves with age plus either one other major criterion (joint contractures of the knee, hip, and elbow and/or hypermobility of distal joints) and/or three of the four minor criteria (soft, doughy skin, motor developmental delay, myopathy on muscle biopsy, atrophic scarring; Malfait et al., 2017).

The thirteenth and last EDS subtype is periodontal EDS (pEDS). Minimal features that suggest pEDS include severe and intractable periodontitis of childhood or adolescent onset or lack of attached gingiva plus pretibial plaques and a family history of a first-degree relative who meets clinical criteria and one minor criterion (easy bruising, distal JH, skin hyperextensibility and fragility and abnormal scarring, increased rate of infections, hernias, Marfanoid facial

features, acrogeria, and prominent vasculature; Malfait et al., 2017). As with other EDS subtypes, some of the minor criteria overlap with hEDS, but the distinctive major features allow clinical distinction from the other subtypes. Confirmatory molecular testing is obligatory to reach a final diagnosis. The molecular basis of pEDS is heterozygous gain-of-function mutations in *C1R* or *C1S*, encoding subunits C1r and C1s of the first component of the classical complement pathway (Malfait et al., 2017).

VIII. Heritable CTD with overlapping features to hEDS

JH may be the result of ligamentous laxity due to a connective tissue disorder or hypotonia related to a neuromuscular condition (Voermans et al., 2008; Colombi et al., 2015; Donkervoort et al., 2015; Castori et al., 2017). As highlighted under the current clinical diagnostic criteria for hEDS, the exclusion of other heritable conditions is important.

For example, Bethlem myopathy is caused by autosomal dominant or recessive mutations in one of three collagen VI genes (Donkervoort et al., 2015). The disorder is characterized by slowly progressive muscle weakness and joint contractures in the fingers and other joints (Voermans et al., 2008; Donkervoort et al., 2015). Characteristic skin findings, described as follicular hyperkeratosis and keloid formation, may also be present (Lampe & Bushby, 2005; Kirschner et al., 2005; Voermans et al., 2008). Symptom onset can vary, ranging from prenatal to mid-adulthood (Voermans et al., 2008; Donkervoort et al., 2015). Ullrich congenital muscular dystrophy (UCMD) is another collagen VI mutation disorder with an autosomal recessive inheritance pattern in most cases (Voermans et al., 2008; Donkervoort et al., 2015). Along with hypermobility of distal joints such as toes, ankles, fingers, and wrists, UCMD has striking features such as curvature of the spine and spinal rigidity as well as respiratory failure (Lampe &

Bushby, 2005; Voermans et al., 2008; Donkervoort et al., 2015). Symptoms tend to onset at birth or in early childhood (Voermans et al., 2008). Because of the wide range of age of onset as well as the presence of joint laxity, myopathies such as these are appropriate differential diagnoses and must be excluded, especially in pediatric patients (Colombi et al., 2015).

Other heritable disorders of connective tissue must also be considered. For example, Marfan syndrome is an autosomal dominant condition caused by pathogenic variants in the *FBN1* gene (Dietz & Pyeritz, 1995; Loeys et al., 2010; Colombi et al., 2015). The combination of moderate JH and a "marfanoid habitus" (described as tall and slender build, arachnodactyly, and/or dolichostenomelia with an arm span/height ratio of ≥1.05) is seen in individuals with Marfan syndrome as well as in about one-third of JHS and hEDS patients (Hakim & Grahame, 2003; Grahame & Hakim, 2013; Colombi et al., 2015). However, if marfanoid features are present, other conditions that share these features, such as Loeys-Dietz syndrome, Stickler syndrome, and homocystinuria, should be considered along with Marfan syndrome (Malfait et al., 2017). Similarly, aortic root dilation may be present in both individuals with Marfan syndrome and those with hEDS. While aortic root dilation does not progress in adulthood in hEDS, it can progress to life-threatening aortic aneurysm or dissection in Marfan syndrome (Judge & Dietz, 2005). Mitral valve prolapse may also be present in both conditions, but it is more common in individuals with Marfan syndrome (Grahame & Hakim, 2013). Some features that can differentiate Marfan syndrome from hEDS include ectopia lentis (ocular lens dislocation) (Colombi et al., 2015; Gensemer et al., 2021), skeletal features, and spontaneous pneumothorax (Grahame & Hakim, 2013). Ophthalmological examinations and echocardiograms are recommended to ensure that the features associated with Marfan syndrome are not present in an individual.

Loeys-Dietz syndrome (LDS) is another disorder that should be considered in the differential diagnosis of JH. LDS is an autosomal dominant condition caused by pathogenic variants in genes involved in TGF-β signaling (Donkervoort et al., 2015; Gouda et al., 2022). The subtypes of LDS are determined by the component that is involved: TGF-β receptor 1 (TGFBR1) for LDS type 1, TGF-β receptor 2 (TGFBR2) for LDS type 2, downstream effector SMAD3 for LDS type 3, TGFB2 for LDS type 4, and TGFB3 for LDS type 5 (Donkervoort et al., 2015; Gouda et al., 2022). LDS is characterized by vascular features, such as aortic aneurysms and dissections, and skeletal findings including scoliosis and arachnodactyly (Donkervoort et al., 2015; Gouda et al., 2022). Because of these features that overlap with Marfan syndrome, they are differential diagnoses of each other. LDS may also present with easy bruising, translucent skin, and atrophic scars along with the vascular involvement (Colombi et al., 2015; Gouda et al., 2022), which may be confused with vEDS (Colombi et al., 2015). With the joint laxity and absence of ectopia lentis (Judge & Dietz, 2005; Colombi et al., 2015; Gouda et al., 2022), LDS may arise as a differential diagnosis of hEDS (Colombi et al., 2015). However, features unique to LDS such as hypertelorism, cleft palate, and developmental delay should help differentiate the two conditions clinically (Colombi et al., 2015).

There are many other inherited CTD that must be distinguished from hEDS and that are not listed above. Since many of these conditions have a known molecular etiology and associated manifestations that require appropriate medical management and surveillance, it is important to rule them out first before considering hEDS as a final diagnosis.

IX. Acquired conditions with features that overlap with hEDS

Some acquired conditions have some features similar to hEDS. Celiac disease (gluten-sensitive enteropathy) is a condition in which consuming gluten (a structural protein naturally

found in wheat and certain other cereal grains) can cause features similar to some that may be associated with hEDS, such as chronic fatigue, bloating, constipation, diarrhea, and abdominal pain, but it does not cause JH (Danese et al., 2011).

Fibromyalgia, a common musculoskeletal disorder that causes joint and muscle pain, also has many features that resemble some of those associated with hEDS, both physically and psychologically. Individuals with fibromyalgia may experience headache, dysautonomia, gastrointestinal problems like diarrhea and constipation, fatigue, and sleep disturbance (Alsiri et al., 2023). However, joint instability, such as dislocations, occurs more frequently in the hEDS population than in those with fibromyalgia (Rombaut et al., 2011). Pathophysiology and biomarkers for fibromyalgia are also unclear, making it difficult to distinguish from hEDS (Alsiri et al., 2023).

hEDS patients may be diagnosed with rheumatological conditions due to joint pain and the overlap of comorbidities like migraine, chronic fatigue, and GI complaints (Rodgers et al., 2017). For example, systemic lupus erythematosus (SLE) is an autoimmune disorder with a broad clinical spectrum ranging from skin manifestations such as a distinctive midfacial rash in a butterfly-shaped distribution to cardiovascular involvement such as cardiomyopathy and heart failure (Ameer et al., 2022). Features of SLE that are similar to comorbidities in hEDS include GI symptoms such as diarrhea and abdominal pain (Ameer et al., 2022). Musculoskeletal manifestations such as arthralgia and arthritis are present in 80% to 90% of patients with SLE, most commonly with symmetrical involvement of small joints such as hands, wrists, and knees, but not with joint laxity. Like rheumatoid arthritis, SLE may present with ulnar deviation and subluxation of the metacarpophalangeal joints (Ameer et al., 2022).

X. Referrals to the Genetics specialty regarding hEDS and other CTD

A referral to a Medical Genetics specialty clinic can be helpful for patients with GJH or features associated with CTD, such as dislocations and skin fragility. In such cases, the medical genetics team will collect a personal and family history, conduct a comprehensive physical examination, refer for additional imaging or exams if needed, and consider appropriate genetic testing options (Ihinger, 2019). If genetic testing is pursued, they will discuss the genetic test results with the patients to explain what the results mean for them and their family members.

However, there are other referrals to Genetics for possible hEDS that may not be appropriate. Having GJH is a required criterion for hEDS diagnosis. Patients should not be referred for evaluation for possible hEDS if they do not have generalized hypermobility. In addition, hEDS may be associated with comorbidities such as POTS or MCAS, but these more commonly occur independent of hEDS; individuals with POTS or MCAS without JH should not be referred for evaluation for hEDS. Individuals who developed a joint dislocation from a specific event, such as an accident or sports injuries, are also less likely to have hEDS.

Knowing how to make an appropriate referral is essential because some patients with certain indications may have life-threatening conditions and may need a genetics evaluation and possibly genetic testing urgently. For example, a personal and/or family history of spontaneous vascular dissection or colon rupture could be an indication of vEDS, which could result in sudden death (Byers et al., 2017). When a diagnosis of vEDS is confirmed, there are management guidelines including surveillance and surgical intervention (Byers et al., 2017) that may help prevent such tragic events. By knowing the key signs and referring the patients appropriately, the medical genetics team will be able to triage cases more efficiently and identify the urgent cases faster.

XI. Gaps in current knowledge and research

The hEDS community faces delays in diagnosis due to different factors such as diagnostic difficulty due to the complexity of hEDS and the lack of molecular confirmation (Anderson & Lane, 2022). The major phenotypic feature of GJH is common in the general population and can be either acquired or inherited. The diagnostic process is complicated by the lack of consensus on how to confirm the diagnosis of hEDS in individuals with GJH (Remvig et al., 2014). The wide range of the phenotypic spectrum, including overlap with other disorders, makes it difficult to diagnose individuals with hEDS accurately. While The 2017 International Classification of the Ehlers-Danlos Syndromes outlines clinical diagnostic criteria for hEDS, the inability to confirm the condition with molecular testing means that it is not possible to determine whether the diagnostic criteria are accurately capturing the true hEDS population or whether it is a single disorder or a heterogeneous one (McGillis et al., 2020). Some individuals may be misdiagnosed with hEDS, and some others who truly have hEDS may not have been diagnosed yet, leading to a patients' diagnostic odyssey and physical and psychological hardships (Halverson et al., 2021). Misdiagnosis can also lead to inappropriate management of the patient. Treatment of hEDS is primarily symptomatic, whereas there may be specific treatments for a similar disorder that would not be given if the diagnosis of that disorder had been missed.

Studies have shown that some non-genetics providers may not be well informed about hEDS or may have "limited, outdated, or incorrect understanding of the condition" (Anderson & Lane, 2022).

Another study used a survey to explore expectations for genetic counseling among patients diagnosed with hEDS (Ahimaz et al., 2022). All 460 participants anticipated education

and psychosocial counseling from genetic counseling sessions, which would also induce positive feelings (Ahimaz et al., 2022). However, there has been limited research regarding what referring providers expect from genetics evaluations of their patients.

The involvement of genetics clinics in serving the hEDS patient population has also been studied. The patient flow through an EDS Genetics Clinic was improved with positive patient satisfaction after implementing a model to provide a questionnaire, an EDS information sheet, and a visit itinerary to new patients (Prakash et al., 2018). In another study, a genetics evaluation for EDS or other CTD was found to be valuable for such patient populations in that they were able to discuss their clinical features and receive comprehensive examinations from geneticists and support, education, and resources from genetic counselors (Ihinger, 2019). In addition, there are other studies on hEDS that revealed a lack of consensus on tests and criteria for clinical diagnosis of hEDS (Remvig et al., 2014), or how to better diagnose individuals with hEDS or other EDS subtypes (Damseh et al., 2022). However, there has not been a study that illustrates the processes by which patients suspected of having EDS are referred to, and triaged by, genetics clinics or, more specifically, what is being sought when referral of these patients is made to the genetics clinic.

The excessive number of referrals for evaluation for hEDS may overwhelm a genetics clinic. Some genetics clinics that are experiencing this phenomenon send a letter to the referring providers to inform them that they no longer see patients with an indication of hEDS unless specific referral criteria are met. Furthermore, referring providers often tell their patients that they are being referred “for genetic testing for hypermobile EDS,” leaving patients disappointed when they learn that no such definitive procedure exists for this disorder. The first step to solving these problems could be to understand how healthcare professionals in fields other than genetics

interact with suspected hEDS patients and what motivates them to refer these patients for a genetics evaluation. This research could help to clarify the current goals of providers who refer patients to genetics clinics for evaluation for hypermobility and to provide direction for clinics regarding how to educate referring providers and how to triage patients more efficiently and improve the ability of the medical system to serve their needs.

XII. Purpose and aims of this study

This study aimed to understand why medical professionals refer patients for genetic evaluation for hypermobility and which features they perceive are likely to represent hEDS. The methodology used was a retrospective chart review of referrals for hypermobility or hEDS to the University of California, Irvine adult genetics clinic including review of the referring providers' relevant medical notes. The goals of the study were (1) to develop classification schemes to recognize appropriate referrals to genetics for hEDS or other CTD, (2) to see what referring providers document when referring patients for a genetics evaluation for hEDS/CTD, (3) to capture a snapshot of why providers from various specialties refer patients to genetics for hEDS or other CTD, and (4) to analyze whether there are factors that could help assist genetics clinics in assessing the appropriateness of a referral.

METHODS

I. IRB approval

This study was reviewed by the University of California, Irvine (UCI) Institutional Review Board (IRB) as protocol number HS# 2023-1318. The research protocol was reviewed under Expedited category 5 with "no more than minimal risk to subjects." The IRB application was submitted on September 26th, 2022, with final approval granted on November 1st, 2022.

II. Retrospective Chart Review

1. Patient population

The study population comprised patients over the age of 18 who were referred between November 2017 and October 2022 to the adult genetics at The University of California, Irvine Medical Center (UCIMC) for an evaluation for hypermobile Ehlers-Danlos syndrome (hEDS) and other referrals related to hEDS/CTD. A list of ICD-9/ICD-10 codes for indications commonly associated with hEDS referrals was created (Table 1; Table 2). The referrals for the patient population of interest were acquired by three different processes:

1) Referrals with the ICD-9/ICD-10 codes of interest that were currently in the electronic medical record work queue to be scheduled in the Adult Genetics clinic.

2) A retrospective search of the electronic medical record for any patients seen in the genetics clinic with a referral made during the study time period and including one or more of the target ICD-9/ICD-10 codes.

3) A retrospective search of the electronic medical record for any patient referred to the genetics clinic during the study time period and including one or more of the target ICD-9/ICD-10 codes, regardless of whether or not the patient had a completed genetics visit.

A total of 54 referrals were obtained from the current Genetics work queue (Process one above). A list of 98 referrals that already had visits to the Genetics clinic with the ICD-9/ICD-10 codes of interest since 11/4/2017 also was obtained (Process two above). Lastly, a total of 484 unique patients were referred to the Genetics clinic with the ICD-9/ICD-10 codes of interest since 11/4/2017, regardless of whether they had a visit at the Genetics clinic or not (Process three above). Of the 484 referrals identified through process three, referrals were collected from

newest to oldest referrals, encompassing referrals that were made from 9/2021-10/2022. Otherwise, referrals older than 9/2021 were included in the two other referral groups.

The referrals that had one or more of the chosen ICD-9/ICD-10 codes that are referring to genetics for EDS, CTD, and/or JH were included in the data (Table 2). Referrals that did not meet IRB protocols or those for returning patients were excluded from the data pool. The referrals that were determined on review to not be referrals for evaluation of hEDS/CTD were also excluded. For the remaining referrals, the associated referring providers' medical notes and documentation that mentioned or led to referral to the genetics clinic were also reviewed if available.

During the data collection process, subject identifiers were kept separately from the research information by generating new, non-identifying numbers for data collection in separate, secure files on a UCI network computer within the secured Health Sciences network. The data were collected in a spreadsheet and used for subsequent analyses.

Table 1: Indications commonly associated with hEDS referrals

Arthralgia
Cardiac arrhythmias
Compression of brain
Ehlers-Danlos syndrome
Dysautonomia
Family history of other diseases of the musculoskeletal system and connective tissue
Fibromyalgia
Hypermobility syndrome/Benign joint hypermobility
Hypermobile Ehlers-Danlos syndrome
Joint derangement
Mast cell activation
Pectus excavatum
Systemic involvement of connective tissue
Systemic lupus erythematosus
Temporomandibular joint disorder

Table 2: ICD-9/ICD-10 codes on referral chosen for data collection

ICD-9 Codes	Code titles
337.9	Unspecified disorder of autonomic nervous system
427.89	Other specified cardiac dysrhythmias
719.40	Pain in joint site unspecified
728.5	Hypermobility Syndrome
756.83	Ehlers-Danlos syndrome
ICD-10 Codes	**Code titles**
D89.40	Mast cell activation, unspecified
G90.1	Familial dysautonomia[a]
G93.5	Compression of brain
I49.8	Other specified cardiac arrhythmias
M24.9	Joint derangement, unspecified
M25.50	Pain in unspecified joint
M26.60	Temporomandibular joint disorder, unspecified
M32.9	Systemic lupus erythematosus, unspecified
M35.7	Hypermobility syndrome
M35.9	Systemic involvement of connective tissue, unspecified
M79.7	Fibromyalgia
Q67.6	Pectus excavatum
Q79.6	Ehlers-Danlos syndromes
Q79.62	Hypermobile Ehlers-Danlos syndrome
Z82.69	Family history of other diseases of the musculoskeletal system and connective tissue

Descriptions from: ICD9Data.com, ICD10Data.com (accessed May 20th, 2023).

[a] Referrals were for dysautonomia but the only ICD10 code available for dysautonomia was for familial dysautonomia.

2. Data points

Patient demographics including age at the time of referral and sex assigned at birth, insurance type, referral year, zip code were collected.

For external referrals, the zip code at the time of the referral was collected if listed on the referral packet. Otherwise, the zip code listed in the electronic medical record at the time of the data collection was collected as proxies for both internal and external referrals. Zip codes were then converted to states and counties, and a map was drawn showing the number of referrals from each region, using an online resource (mapchart.net).

The following data were collected for each referral: ICD-9/ICD-10 codes associated with the referral, CPT procedure codes, referring provider's specialty, referral source (external/internal), referral priority, and the wording and writing of the referral indication (internal referral only). From the medical documentation by the referring provider, the following were collected: chief complaints, wording and writing of the referral indication by the referring provider, whether the patient requested to be referred to the genetics clinic, any relevant family history (e.g., hypermobility, CTD-related features, EDS, vascular rupture), the presence or absence of hypermobility assessments, Beighton score if measured and recorded, whether they were diagnosed with EDS (patient reported or documented under diagnoses), physical examination and relevant clinical features evaluated and/or present (including but not limited to hypermobility, joint dislocations, marfanoid features, sleep disturbance, fatigue, functional gastrointestinal disorders, anxiety, depression, musculoskeletal pain, headache, fibromyalgia), and possibly relevant injury/surgical/accident history and medical history. Physician's notes or documentation that is relevant to the study was also collected, including the physician's documentation pertaining to hEDS/CTD, common conditions that are frequently associated with

hEDS (e.g., POTS, dysautonomia, mast cell activation, or possibly relevant past/current medical history), any relevant note of patient-self-report (e.g., diagnosis of EDS, features they think they have, the desire for referral to the genetics clinic), and referring physicians' plans for the patient.

Some features were collected from the detailed notes taken after reviewing the medical records. Those features include arthralgia, myalgia, musculoskeletal pain, myofascial pain, joints "popping in and out," double jointed, unstable joints, loose joints, joint/ligament laxity, marfanoid habitus/tall/thin habitus, multiple fractures, ligament/tendon tears, and sprains. The features were noted if they were present or explicitly documented as absent. Some features noted in a referral may be excluded from the results due to lack of details. For example, if the note said "constant pain" but was unclear as to whether this was joint or musculoskeletal pain, this feature was not noted as either present or absent and was not included among the counts of features.

3. Classification of referral appropriateness

Categories of referral appropriateness were developed through a consensus process with the thesis committee. A flowchart was also created to classify appropriateness consistently (Appendix A).

4. Grouping referral indications

After reviewing the referral documentation, a list of possible referral indications was derived from the data (Table 3). For each referral, it was noted whether each of these referral indications was explicitly listed as a primary reason for referral to the genetics clinic. In some cases, a potential referral indication was listed in the documentation accompanying a referral without being specifically identified as a referral indication; these were separately noted. For

example, any notes under the referral indication section of the referral were considered as primary reasons for the referral. Similarly, any notes followed by the statement "Refer to genetics for…" were also considered as referral indications. See Appendix B for specific examples of various scenarios regarding how the determination was made.

Some indications that were suspected to possibly be inappropriate such as a patient requested referral, patient suspected EDS (which would require physician assessment), and features commonly associated with CTD (e.g., pain, POTS) were assessed to see whether they were found in combination with more appropriate indications such as JH and CTD-suspected history (e.g., joint dislocations, skin findings).

Table 3: 11 categories of possible referral indications

1. Evaluation for possible CTD or Rule out CTD
2. Evaluation for possible EDS or Rule out EDS
3. Patient requested referral
4. Patient concerned/suspected EDS
5. "Patient has been told by other providers that they have EDS" or "there has been concern for EDS"
6. Hypermobility or joint laxity
7. CTD-suspected history (e.g., joint dislocations, skin findings)
8. Features commonly associated with CTD (e.g., pain, POTS).
9. EDS diagnosis or Has EDS
10. Genetic testing or For testing
11. Family history of CTD/EDS

5. Grouping ICD-10 codes

Each ICD-10 code that was associated with a referral was grouped into one of six categories: CTD, CTD-related features, possibly CTD/EDS-related features, features commonly associated with hEDS, nonspecific features, and unrelated to hEDS. The "CTD" category consists of ICD-10 codes used when individuals have the diagnosis of a condition such as EDS, hEDS, or Marfan syndrome. Under the category "CTD-related features" are those that can be features of CTD, such as aortic aneurysm or dissection and pneumothorax. "Possibly CTD/EDS-related features" includes musculoskeletal features that are among the hEDS diagnostic criteria, such as joint dislocations that would indicate the presence of JH. Any features that are not among the diagnostic criteria but are comorbidities with hEDS (e.g., POTS, dysautonomia, MCAS) are grouped together under "features commonly associated with hEDS". Features that may be seen in individuals with CTD but are not specific enough (e.g., "skin change") and those that are unrelated to CTD were categorized as "nonspecific features" and "unrelated to hEDS," respectively.

III. Data Analyses

IBM SPSS Statistics (IBM Corp. Released 2021. IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp) was used for data analyses. Patient demographic characteristics such as age and sex and referral characteristics such as year of referral, referring providers' specialties, ICD-10 codes and CPT codes associated with the referrals, clinical features documented, and referral indication type were assessed using counts and percentages. The priority level that was indicated on each referral was classified as routine or higher priority (including stat, urgent, and emergency). Pearson chi-square statistics were calculated to measure

the significance difference in referral appropriateness among sex assigned at birth, referral source, referral priority, specialty of referring provider, and insurance types. For these analyses, referral appropriateness was grouped into two groups: appropriate referrals vs. other classifications including context-dependent, missing-detail, and inappropriate referrals. The distribution of all four categories of referral appropriateness (appropriate, context-dependent, missing-detail, and inappropriate) was also compared. For this exploratory study, the significance for each statistical test is expressed using a nominal p-value, and no correction has been made for multiple comparisons.

RESULTS

I. Referrals included in analysis

The referrals were excluded from the data if they did not meet IRB protocols, were follow-up referrals, or did not have referring providers' clinical documentation. A total of 54 patients were obtained from the Genetics work queue, and 44 of them were included in data analyses (Table 4; Appendix C). There were 98 referrals that had visits to UCIMC Genetics with ICD-9/ICD-10 codes of interest. Out of the 98 referrals, 43 referrals were included in the data set. Lastly, a total of 484 unique patients were referred to Genetics with the ICD-9/ICD-10 codes of interest since 11/4/2017, of which 229 referrals from 9/2021-10/2022 were evaluated, and 135 referrals were included in further analyses (Table 4; Appendix C). The remaining 255 referrals from 11/2017-8/2021 from the list of 484 referrals were not evaluated due to the limitation of time, unless they were previously reviewed referrals included in the Genetics work queue and the referrals that had visits to UCIMC Genetics. All together, 143 referrals were referrals for hEDS or other possible CTD that either had clinical documentation or sufficient material provided in

the referral indication section to classify for appropriateness and to analyze further. The numbers of referrals received and included in data analyses from each of the three data sources are shown in Figure 1, which also presents how many referrals came from only one of the three groups, and how many were from two groups. The details on the number of referrals that met the IRB protocol as well as the number of referrals that were excluded and why are listed in Appendices C-G.

Table 4: Number of referrals received, reviewed, and included in data analyses by referral sources.

Referral source	Received	Reviewed	Included in analyses
Referrals that were on the work queue	54	54	44
Referrals with visits to UCIMC Genetics with ICD-9/ICD-10 codes of interest	98	98	43
Referrals to Genetics based on ICD-9/ICD-10 codes of interest since 11/4/2017	484	229[b]	135
Total	—	259[c]	143[a]

[a] Some referrals were from two groups. See Figure 1 below for detail.
[b] Data from this set of referrals were collected from newest to oldest referrals, encompassing referrals that were made from 9/2021-10/2022. Otherwise, referrals older than 9/2021 were included in the two other referral groups. See Appendix C.
[c] See Appendix D for number of referrals overlapped in two groups.

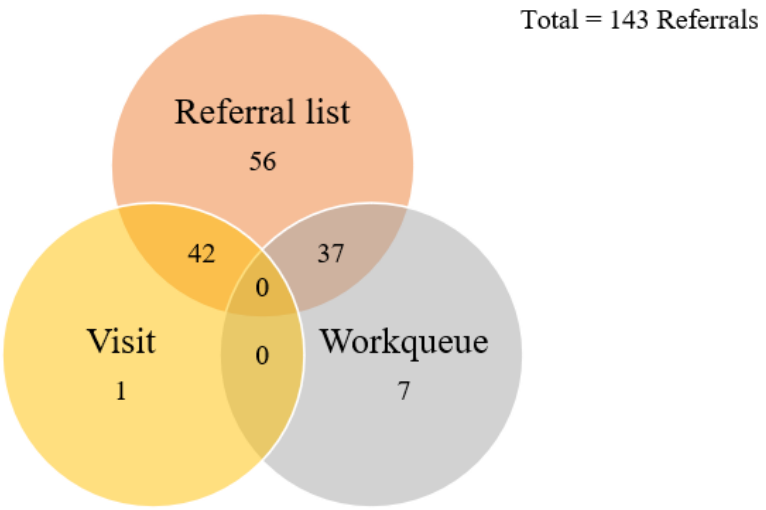

Figure 1: Number of referrals included in data analyses distributed by referral sources. The three groups of referrals are: Referrals that were on the work queue ("Work queue", colored in gray venn diagram), referrals with visits to UCIMC Genetics with ICD-9/ICD-10 codes of interest ("Visit", colored in yellow), and referrals to Genetics based on ICD-9/ICD-10 codes of interest since 11/4/2017 ("Referral list", colored in orange). 7 referrals were only from the "Work queue," 1 referral was only from the "Visit," and 56 referrals were only from the "Referral list." 37 referrals were from both the "Work queue" and the "Referral list," and 42 referrals were on both "Visit" and "Referral list." In total, 143 referrals were included in data analyses.

II. Referral characteristics

1. Referral years

The number of referrals included in the analysis data set, by year, was counted from November 2017 to October 2022 for the 143 referrals (Table 5; Appendix H).

Table 5: Number of hEDS/CTD referrals included in the data set, by year

Year	N=143
	N (%)
Nov-Dec 2017	2 (1.4)
2018	9 (6.3)
2019	6 (4.2)
2020	14 (9.8)
2021	37 (25.9)
Jan-Oct 2022	75 (52.4)

* The referral numbers do not reflect all referrals to the genetics clinic since November of 2017.

2. Age and sex assigned at birth

The range of patients' ages at the time of referral was 18-77 years with a mean age of 34.3 years (Table 6; Appendix I). More specifically, 38% (N=54) of patients were in their 20s, and 32% (N=46) were in their 30s. For comparison, the age distribution in the general population for Los Angeles and Orange counties is shown in Figure 2, with 18% in their 20s and 20% in their 30s (U.S. Census Bureau, 2021).

Table 6: Ages of patients reviewed

Age	N=143
Min-max	18-77
Mean/SD	34.3/11.7
Age groups	N (%)
18-19	4 (2.8)
20-29	54 (37.8)
30-39	46 (32.2)
40-49	24 (16.8)
50-59	9 (6.3)
60-69	5 (3.5)
70-77	1 (0.7)

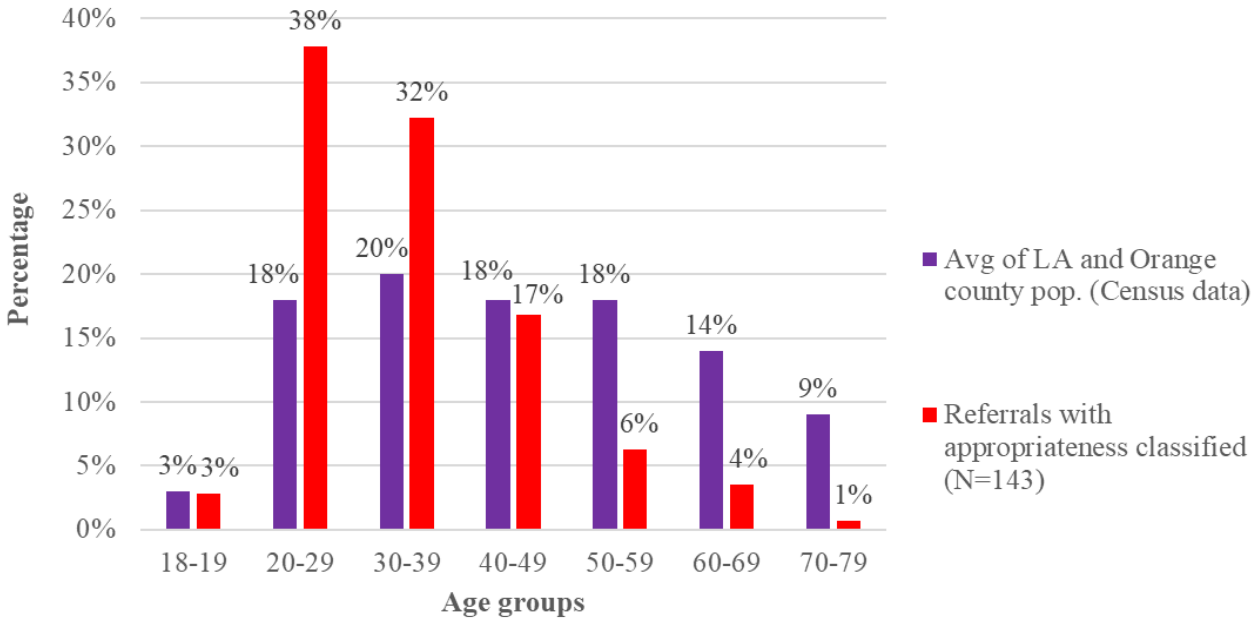

Figure 2: Age distribution comparison with general population. The distributions of different age groups among referrals that had their appropriateness classified (red) were calculated into percentages and compared to the average distribution based on averaging Los Angeles and Orange County populations, also represented in percentages (purple; U.S. Census Bureau, 2021). There were more individuals in their 20s and 30s among the referrals than what would be expected based on the general population distribution.

The majority of patients (N=125, 87.4%) were female (Table 7; Appendix I). Relative to the general population with the female:male ratio of 50:50, the referrals have a higher proportion of females (Figure 3; U.S. Census Bureau, 2021).

Table 7: Sex (assigned at birth) of patients reviewed

Sex	N=143
	N (%)
Female	125 (87.4)
Male	18 (12.6)

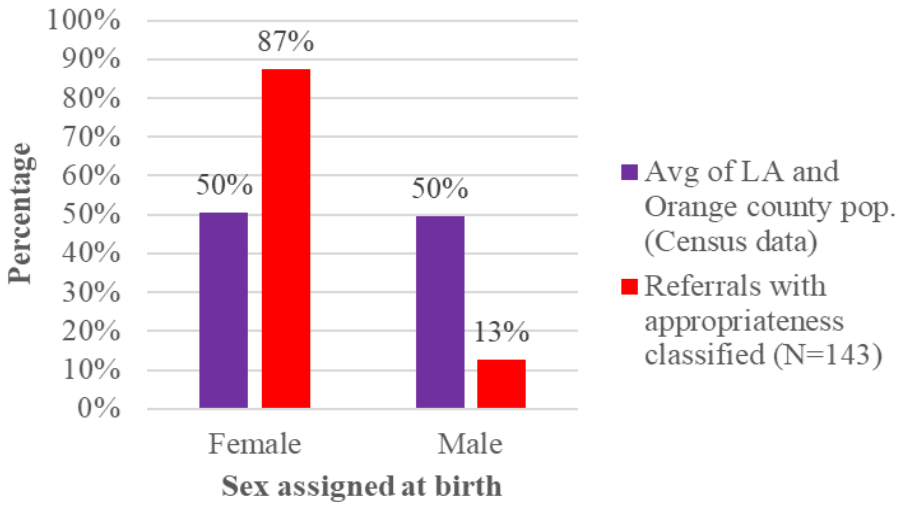

Figure 3: Sex (assigned at birth) distribution comparison with general population. The distribution of sex (assigned at birth) in referrals that had their appropriateness classified (red) was calculated into percentages and compared to the distribution of sex based on averaging Los Angeles and Orange County populations, also represented in percentages (purple; U.S. Census Bureau, 2021). There were more females among the referrals than what would be expected based on general population distribution.

3. *Insurance information*

The type of primary insurance coverage information was collected and analyzed by classifying as Commercial or Federal and by further subclassifications within each group (Table 8). Information regarding dual coverage was not collected for this study. The majority of patients (N=88, 61.5%) had commercial insurance (Table 8; Appendix J). The most common among the types of commercial insurance was Preferred Provider Organization (PPO), which does not require authorization (N=63, 44.1%; Table 8). The most common among the federal insurances was Medi-Cal (N=28, 19.6%; Table 8).

Table 8: Insurance types associated with analyzed referrals

Insurance		Authorization needed?	N=143 N (%)
Commercial	Preferred Provider Organization (PPO)	No	63 (44.1)
	Health Maintenance Organization (HMO)	Yes	18 (12.6)
	Exclusive Provider Organization (EPO)	Yes	3 (2.1)
	Licensed Only Agents (LOA)	Yes	1 (0.7)
	High Performance Network (HPN)	Yes	1 (0.7)
	Point of Service (POS)	Yes	1 (0.7)
	Third Party Administrator (TPA)	Yes	1 (0.7)
Commercial (Total)			88 (61.5)
Federal	Medi-Cal	Yes	28 (19.6)
	Medicaid	Yes	12 (8.4)
	Medicare (A&B)	No	6 (4.2)
	Medicare (Managed)	Yes	3 (2.1)
	Tricare	Yes	6 (4.2)
Federal (Total)			55 (38.5)

4. Residing county

The University of California, Irvine Medical Center (UCIMC) is located in Orange County. Most of the patients resided in Orange County, California (N=79, 55.2%) at the time of the referral; the zip code at the time of data collection was used if the zip code at the time of referral was not available (Table 9; Appendix K). Many other referrals also came from neighboring counties, such Los Angeles County (N=27, 18.9%), Riverside County (N=12,

8.4%), San Bernardino County (N=11, 7.7%), and San Diego County (N=6, 4.2%; Table 9; Figure 4). There were two referrals for patients from Northern California: Mendocino and Marin Counties (Table 9). While the majority of the patients (N=140, 97.9%) are from California, there were three referrals from out of state. It is important to note that they would have had to be physically in California at the time of an appointment in the UCI Genetics clinic (even if the appointment was by telemedicine).

Table 9: County of Residence for patients referred to the Genetics clinic

State	**County**	N=143
		N (%)
California	Orange	79 (55.2)
	Los Angeles	27 (18.9)
	Riverside	12 (8.4)
	San Bernardino	11 (7.7)
	San Diego	6 (4.2)
	Ventura	2 (1.4)
	Marin	1 (0.7)
	Mendocino	1 (0.7)
	San Luis Obispo	1 (0.7)
California (Total)		140 (97.9)
Nevada[a]	Clark	1 (0.7)
Texas[a]	Travis	1 (0.7)
Washington[a]	King	1 (0.7)

[a] Patient address was outside of California at the time of the referral or data collection. However, they would have had to be in California for their visits.

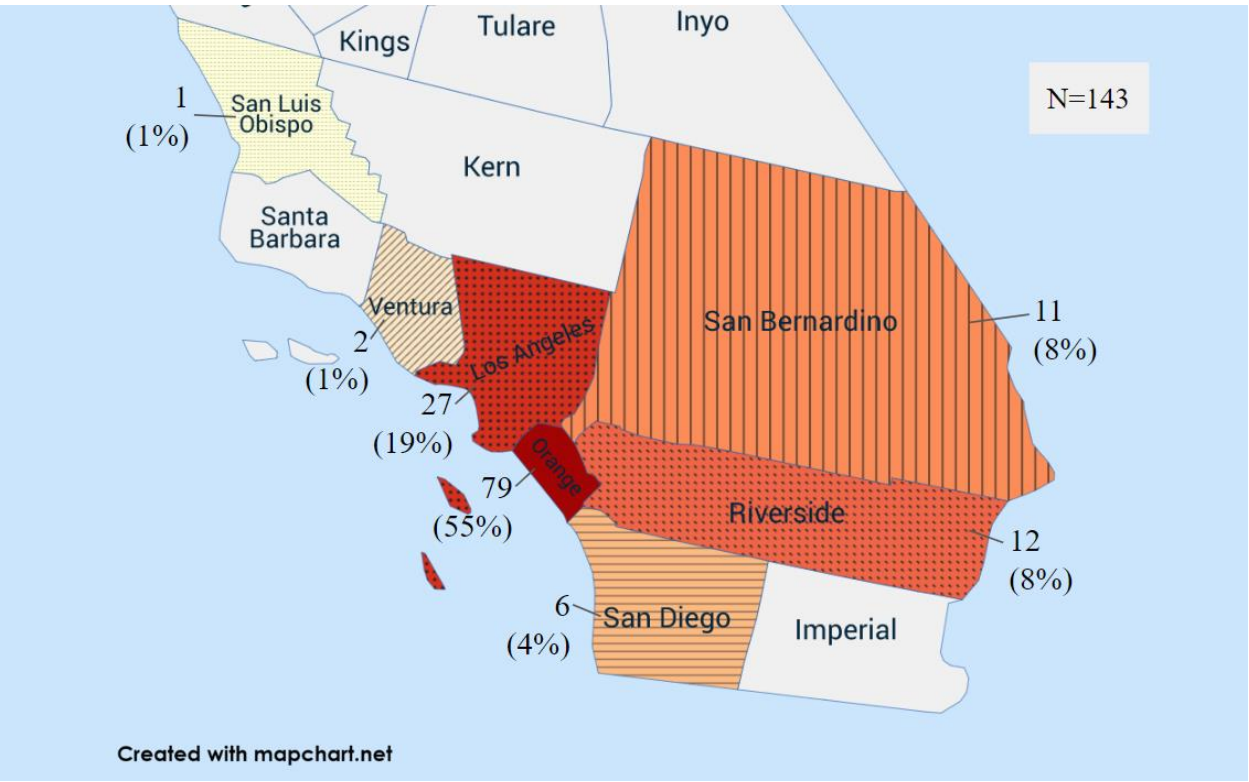

Figure 4: County of Residence for patients referred to the Genetics clinic. Over half (N=79, 55%) of individuals referred to Genetics were located in Orange County. Relevant counties not included in the map are: Marin (CA), Mendocino (CA), Clark (NV), Travis (TX), and King (WA). Mapchart.net was used for the creation of this map.

5. *Referral source and priority*

Referral distribution was summarized by referral source—internal (within UCIMC) vs. external (community providers) and by priority. Of the referrals, 40.6% (N=58) were internal, and the remaining 59.4% (N=85) were external referrals (Table 10; Appendix L). The majority of the referrals (N=127, 88.8%) were prioritized into routine, followed by urgent (N=8, 5.6%), emergency (N=5, 3.5%), and stat (N=3, 2.1%; Table 10; Appendix L).

Table 10: Referral source and priority

Referral information		N=143
		N (%)
Referral source	Internal	58 (40.6)
	External	85 (59.4)
Referral priority[a]	Routine	127 (88.8)
	Stat	3 (2.1)
	Urgent	8 (5.6)
	Emergency	5 (3.5)

[a] The categories are listed in order of increasing priority.

6. Specialty of referring provider

Referrals for EDS and CTD to genetics sent by 17 different specialties were included in this research (Appendix M). When divided into primary care vs. specialty, the majority (N=88, 61.5%) of the referrals were from specialty clinics (Table 11). Referrals from rheumatology were the most frequent, with 55 referrals (39%), followed by family medicine with 38 referrals (27%), and internal medicine with 16 referrals (11%; Figure 5). See Appendix M for the full list of specialties, the distribution of referrals among the specialties, and the groupings of primary care vs. specialty clinics.

Table 11: Primary care vs. specialty clinic referrals

	N=143
	N (%)
Primary care	55 (38.5)
Specialty	88 (61.5)

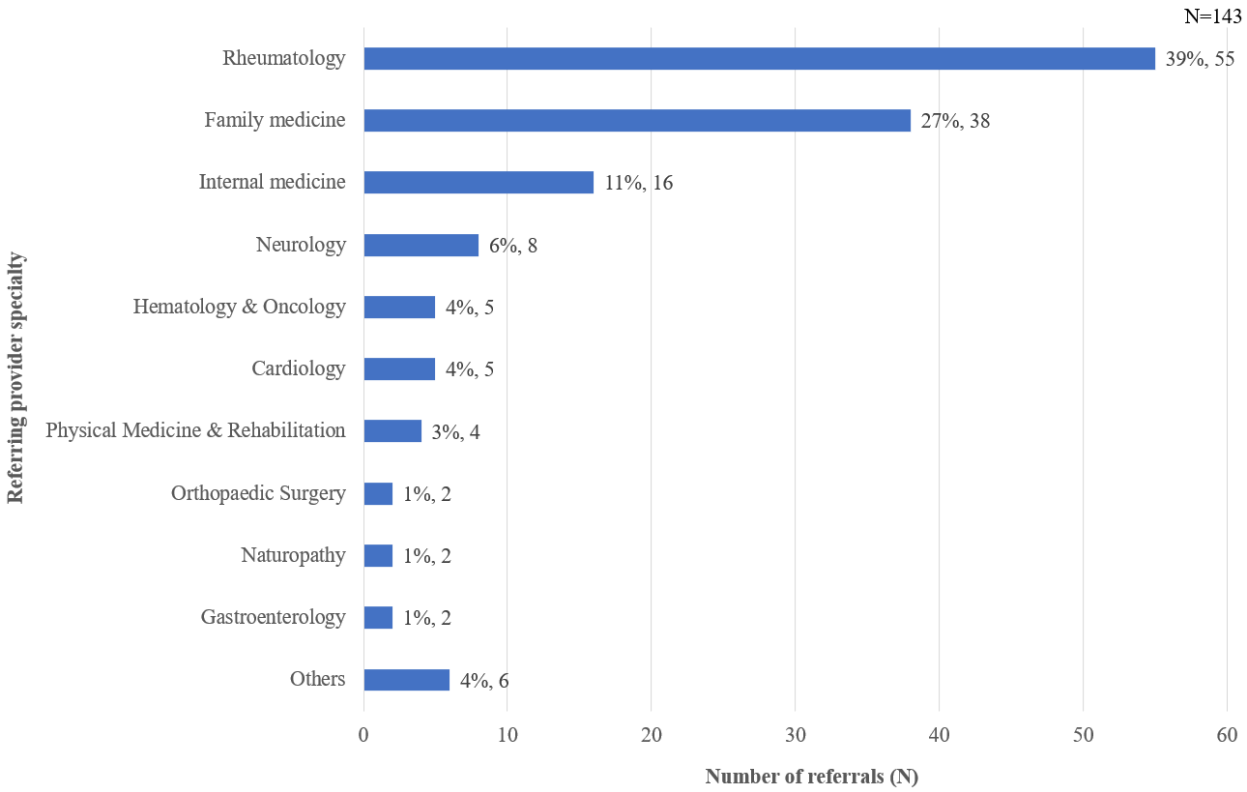

Figure 5: Number of referrals by referring provider specialty. 17 different specialties sent referrals to Genetics for EDS/CTD evaluation. 39% (N=55) of the referrals were from rheumatology, followed by 27% (N=38) family medicine, 11% (N=16) internal medicine, 6% (N=8) neurology, 4% (N=5) hematology and oncology, 4% (N=5) cardiology, 3% (N=4) physical medicine & rehabilitation, 1% (N=2) each of orthopedic surgery, naturopathy, and gastroenterology. Specialties under "Others" are: <1% each of pulmonary medicine, pediatrician, otolaryngology, OBGYN, perioperative care, and allergy and immunology (Appendix M).

7. Associated ICD-10 codes and CPT procedure codes

The ICD-9, ICD-10, and CPT codes associated with the referrals were analyzed. Although the referrals were identified by using the ICD-9 and ICD-10 codes, only ICD-10 codes were looked at for analysis because each ICD-9 code associated with the referrals also had a corresponding ICD-10 code associated with it. Duplicate ICD-10 codes in the same referral were deleted so that the same ICD-10 code within a referral was counted only once. The number of

ICD-10 codes per referral ranged from 1-9, with the mean being 1.60, and that of CPT codes ranged from 1-6 with the mean of 1.65 (Table 12; Appendices N and O).

Table 12: Number of ICD-10 and CPT codes per referral

	ICD-10 codes	CPT codes
No. of ICD-10 codes and CPT codes per referral	N=143	N=143
Min-max	1-9	1-6
Mean	1.60	1.65
No.	N (%)	N (%)
1	95 (66.4)	77 (53.8)
2	30 (21.0)	47 (32.9)
3	9 (6.3)	15 (10.5)
4	4 (2.8)	2 (1.4)
5	3 (2.1)	—
6	—	2 (1.4)
7	1 (0.7)	—
8	—	—
9	1 (0.7)	—

III. Aim #1: Develop classification schemes to recognize appropriate referrals for hEDS or other CTD

1. Categories for referral appropriateness classification

Each referral was classified into one of the four groups: appropriate, context-dependent, missing details, or inappropriate/misinformed. Each category is defined below in Table 13. The

categories and definitions were developed by an iterative consensus process, through discussion between the members of the research team. The initial intention was to categorize each referral as appropriate, context-dependent, or inappropriate/misinformed. However, an additional category was developed to differentiate among the referrals that were lacking in details. Ultimately, "context dependent" referrals were those which were more likely to be appropriate with at least one documented hEDS/CTD criterion (but were missing some context that would be necessary to determine appropriateness). Referrals classified as "missing details" lacked the detail necessary to determine whether any hEDS/CTD criteria were met. A decision-making flowchart was then developed by adapting the hEDS diagnostic criteria checklist and incorporating the four categories (The Ehlers Danlos Society; Appendix A). A decision on the appropriateness classification for each referral was made based on documented factors such as the presence of GJH, CTD-related features (e.g., frequent dislocations, skin findings such as easy bruising, poor wound healing, tissue fragility, artery dilation and/or ruptured artery/hollow organ, family history of CTD), and other comorbidities commonly associated with CTD that are not among the hEDS diagnostic criteria (e.g., POTS, headache, fatigue).

Table 13: Definitions of four categories for referral appropriateness classification

Categories	Definitions
Appropriate	● Multiple features of CTD that meet the diagnostic criteria of hEDS[a] or are seen in other CTD, or ● A single feature of any of the following (in the setting of CTD): ○ Aortic dissection and/or organ rupture ○ Meets Beighton criteria ○ Recurrent dislocations or subluxation in multiple joints and/or tears in multiple musculoskeletal tissues ○ Genetic test result with a pathogenic variant/variant of uncertain significance (VUS)[b] in genes associated with CTD ○ First-degree relative with aortic dissection or organ rupture
Context-dependent	● Meets just one criterion of hEDS[a] or has a feature seen in other CTD, and ○ No other details provided, or ○ Having a CTD-related feature(s) but no details (e.g., chronic joint/musculoskeletal pain (i.e., arthralgia), dislocations, family history) ● Multiple CTD-related features but also with other possible explanation (e.g., sports injuries)
Missing details	● Documentation that other providers suspected EDS, but no details provided ● Having a CTD-related feature(s) but no details provided (e.g., unassessed joint hypermobility, joint/musculoskeletal pain, dislocations – must be in multiple joints/sites)
Inappropriate	● Referral/documentations without any features of CTD that are among the diagnostic criteria

[a] Incorporated The 2017 International Classification of the Ehlers-Danlos Syndromes (Malfait et al., 2017).
[b] A variant of uncertain significance (VUS) is a variation in a genetic sequence identified in a patient's genome for which it is unclear as to whether it has impact on health due to a lack of research or information regarding the variant (NHGRI, accessed May 14th, 2023).

2. *Referral appropriateness classification distribution*

Of the 143 referrals, 58 referrals (41%) were classified as appropriate, 29 (20%) as context-dependent, 45 (31%) as missing details, and 11 (8%) as inappropriate (Figure 6). It is important to recognize that referrals that were classified as inappropriate truly may be inappropriate if the documented features are the only features that the patients had. Alternatively, some of the referrals classified as inappropriate may be lacking documentation of features that are in fact present and would have supported the referral had they been included.

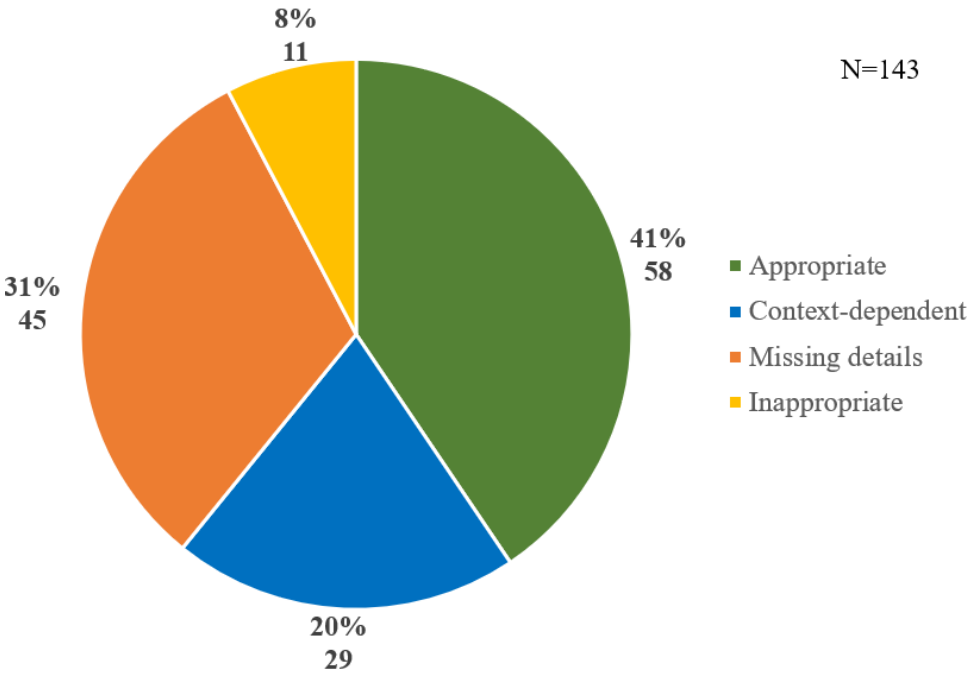

Figure 6: Distribution of referral appropriateness classification. Referrals were classified based on the appropriateness into 4 categories: appropriate, context-dependent, missing details, and inappropriate. See Table 13 above for detailed definitions of each group. A little over half (N=74, 51%) of the referrals were lacking in details.

IV. Aim #2: Documentation included in referrals to Genetics for hEDS/CTD

1. *Features*

The number of referrals that documented each clinical feature was collected. The data included features that are part of the criteria for CTDs or are strongly associated with CTD and

whether referring providers mentioned them in their documentation of the visit that led up to the referral and/or in the referral indications. Data collection included documenting whether the referring provider assessed the feature and found it to be present (i.e., "positive") in the patient, and a separate count was made of whether the referring provider assessed the feature and found it to be absent (i.e., "negative") in the patient. See Appendix P for the full list.

The minimum number of features referring providers assessed was 0 features, and that of recorded positive features was also 0 (Table 14). An example of a referral for which the referring provider did not document any relevant clinical features is one for which the patient had a CTD-related genetic test result that they wanted to review with the genetics team. The maximum number of features assessed by the referring providers and that of documented positive features was 17 features and 15 features, respectively. The medians were six for the number of features assessed by referring providers and four for documented positive features (Table 14).

The majority (N=84, 58.7%) of referrals documented JH as present in their patients (Figure 7). This includes all types of JH ranging from localized to generalized JH. Of the 84 referrals for patients with JH, there were 74 referrals (51.7%) with available clinical documentation about the referring provider's assessment on JH (Table 15). Of those 74 referrals, 37.8% did not assess or document which joints were affected. Only a third (N=25, 33.8%) of the referrals reported Beighton scores, of which 72% (N=18) met the Beighton criteria of 5 points or higher. All individuals in this group were age 50 or younger, except for one individual in their 60s (Data not shown). All individuals who did not meet the Beighton criteria of 5 points or higher (N=7, 28% among referrals with reported Beighton score) were below age 50 (Data not shown). Approximately half (N=72, 50.3%) of the referrals documented the presence of joint pain. Other symptoms that were more commonly recorded as present are abdominal pain/GI

issues (N=53, 37.1%), POTS (N=20, 14.0%), and fatigue (N=41, 28.7%). Among the referrals that did not specifically mention the presence of CTD-related features, few specifically documented the absence of such features, including whether JH was absent (N=6, 4.2%).

Table 14: Number of features assessed per referral

	No. of features assessed (N=143)	No. of positive features (N=143)
Min-max	0-17	0-15
Median	6	4

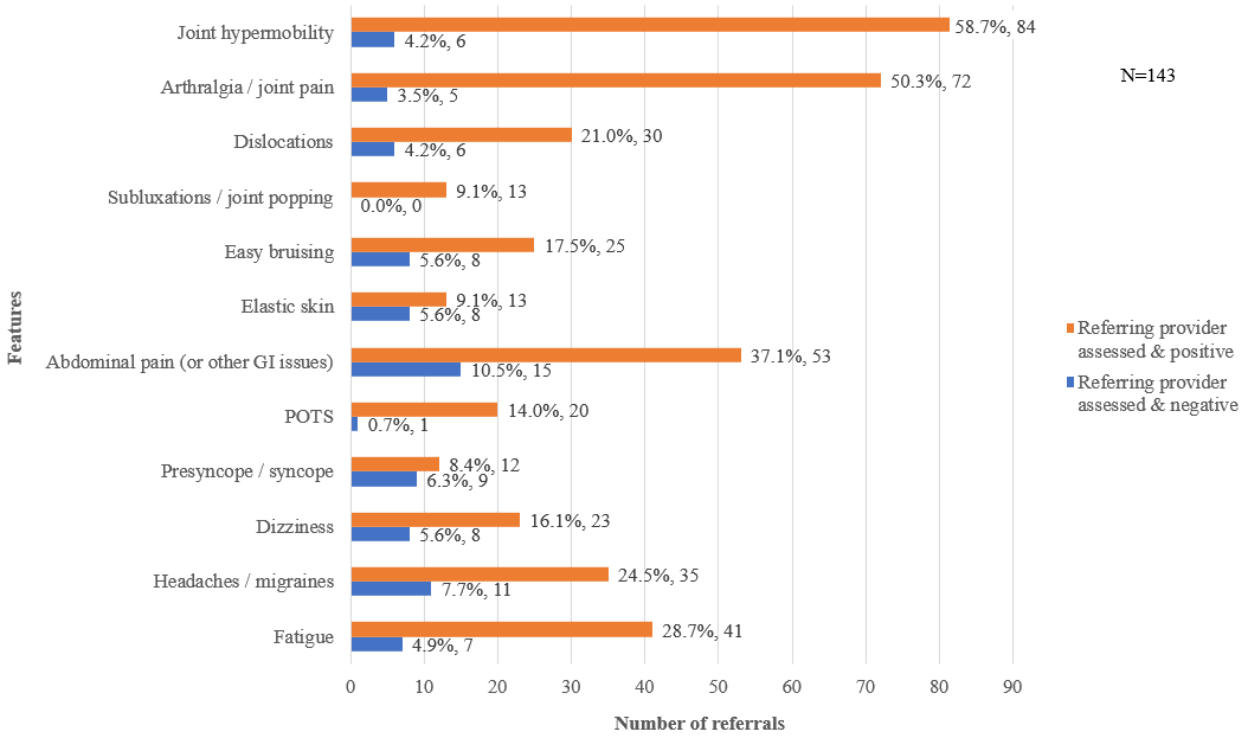

Figure 7: Counts of clinical features referring providers assessed. The numbers of features that are characteristic of or strongly associated with CTD and that were mentioned in the clinical documentation and/or referral indications were collected. Orange represents the number of referrals in which the providers specifically noted that the feature was present in the patient. Blue denotes the number of referrals in which the provider specifically noted that the feature was absent in the patient.

Table 15: Referring providers' assessment on joint hypermobility

Joint hypermobility (JH) noted in clinical documentation	N=143 74 (51.7%)
Referring provider assessment of JH	N=74
No assessment/specific locations of JH	28 (37.8%)
Assessment/specific locations of JH	46 (62.2%)
Assessment similar to Beighton test but without scores[a]	36 (48.6%)
Reported Beighton score	25 (33.8%)
Met Beighton[b]	18 (24.3%)
Did not meet Beighton[b]	7 (9.5%)

[a] Some providers seemed to have asked a few questions from the Beighton criteria (e.g., Can bend forward and place the palms of hands flat on the floor in front of feet without bending knees), but did not report a score or unclear whether they assessed all nine points of the criteria.
[b] The cut-offs for Beighton scale are ≥5 for pubertal adults that are 50 years of age or younger, and ≥4 for those older than age 50. There are additional questions to ask for any Beighton score that is one point below age- and sex-specific cut off, but that was not considered in this assessment.

2. *Examples of referring providers' apparent understanding or misunderstanding of hereditary generalized joint hypermobility disorders*

Along with features, documentation with respect to hEDS and other CTD was collected verbatim. A rigorous qualitative analysis was not done on this captured text, but observations were made.

Some examples of clinical documentation demonstrated good understanding of JHS and hEDS. One rheumatologist wrote:

> "Hypermobility syndrome is diagnosed through clinical examination and laboratory tests used to rule out other disorders that may cause multiple-joint hypermobility. I strongly suggest you review the following information: …"

This provider then included a link to a website with a description of hypermobility syndrome and a fact sheet regarding hypermobility in the realm of rheumatology. Another rheumatologist included in their discussion section of their clinical documentation the following statement :

> “On exam today there is hypermobility of several joints without any synovitis. Rheumatologic review of systems is otherwise unremarkable aside from diarrhea. At this time there is low suspicion for inflammatory arthropathy.”

Among the internal referrals that were patient-requested, an interchange of messages between a patient and his/her provider was captured in the electronic medical record system:

> Patient: "While reading about EDS, it seems like many of my symptoms can be explained by the disorder. The possibility of vascular type EDS is especially troubling. Did the blood tests you ordered include genetic markers that could help determine if I specifically have the vascular type EDS?"
>
> Doctor: "The vascular subtype of EDS does not usually result in significant joint hypermobility which is why I did not think you had this subtype. I do not perform genetic testing but I will refer you to genetics so they can determine if you need additional testing. "

A referring provider documented the pertinent positives and negatives in a patient as the following:

> “Patient does exhibit hyperextensibility of joints with a Beighton scale score of 6. However, she does not have hyperextensibility of the skin, vascular issues, or internal organ rupture.”

As much as there was clinical documentation that suggested a good understanding of JHS/EDS and their diagnostic processes, there was also documentation that may suggest misunderstanding of EDS. A rheumatologist made the following comment in his/her clinical documentation:

> "Suspect EDS type 1 over benign hypermobility type 3 due to frequent joint dislocations."
>
> [Note that frequent joint dislocations are a feature of hEDS and would not cause a higher suspicion of type 1.]

A provider from family medicine made the following comment under the assessment section:

> "Discussed referral to genetics who can look further into her symptoms and order appropriate testing and imaging. Patient requested an echo, but agreed to wait until after meeting with genetics."
>
> [Note that a referral for echocardiogram would be appropriate at the same time as a referral to genetics].

A rheumatologist documented under the patient's History of Present Illness:

> "Patient reports being diagnosed with Ehlers-Danlos syndrome (type III, confirmed by genetic testing) in 2019."

In the clinical note of another patient said:

> "Patient reports being diagnosed with Ehlers-Danlos syndrome 2/2021 .... Mentions completing genetic testing."
>
> [For these two examples, note that there is no molecular genetic testing available for hEDS (i.e., EDS type III)].

There was also documentation that captured some patients' experience with their medical journeys. The following was documented in the clinical note from a family medicine practitioner regarding what his/her patient had shared during the appointment:

> "Hypermobility since childhood. So worried Ehlers Danlos. Has done a lot of reading on topics."

A clinical documentation of a patient with joint pain and muscle aches recorded:

> "[Patient] feels like has been dismissed by other providers."

V. Aim #3: Capture a snapshot of why providers from various specialties refer patients to genetics for hEDS or other CTD

Each referral was assessed for whether any of the 11 possible referral indications were documented as primary referral indications (Table 3). If they were not explicitly written as the reason for referral, a check was then made to determine if they were mentioned in the documentation accompanying the referral. The majority (N=86, 60.1%) of the referrals were to evaluate for or rule out EDS (Table 16). More than a half (N=87, 60.9%) of the referrals either stated JH to be the reason for the referral to genetics or mentioned JH in their clinical documentation along with EDS/CTD.

The referral indications that are less likely to be appropriate (e.g., Patient requested referral, common comorbidities of CTD) were checked if they were found in combination with more appropriate referral indications (e.g., JH, CTD-related features). Among the referrals with the indication of patient-requested referrals (N=21, 14.7%), 10 (37.0%) did not include more appropriate indications such as document CTD-related features or JH (data not shown). Among the referrals with the indication of patients having features commonly associated with CTD (N=65, 45.5%), 10 (15.4%) did not include more appropriate indications such as CTD-related features or JH (data not shown). Testing for EDS was listed as a reason for referral for 18 referrals (12.6%), and two referrals (1.4%) mentioned testing for EDS (Appendix Q). See Appendix Q for further breakdown of the sections “Previous diagnosis of JHS or EDS”, “Genetic testing for CTD/EDS”, and “Family history”.

Table 16: Referral indications

Possible indications	Primary indication for referral to genetics (e.g., "Refer to genetics for…")[a, b] N=143 N (%)	Mentioned in referring provider's clinical documentation[a, b] N=143 N (%)
Evaluation for/rule out CTD	18 (11.2)	5 (3.5)
Evaluation for/rule out EDS	86 (60.1)	8 (5.6)
Patient requested referral	19 (13.3)	8 (5.6)
Patient suspected EDS/CTD	5 (3.5)	16 (11.2)
Patient has "been told they have EDS"/there has been concern for EDS	2 (1.4)	13 (9.1)
Joint hypermobility (JH)	60 (42.0)	27 (18.9)
CTD-suspected history (e.g., dislocations, easy bruising)	34 (23.8)	35 (24.5)
Common comorbidities of CTD (e.g., pain, POTS)	32 (22.4)	33 (23.1)
Previous diagnosis of JHS or EDS	8 (5.6)	9 (6.3)
Genetic testing for CTD/EDS	34 (23.8)	11 (5.6)
Family history	23 (16.1)	12 (8.4)

* The percentages add up to more than 100% because some referrals included more than one indication.

[a] Each of the 11 possible indications was assessed in each referral to determine whether it was a primary referral indication, or whether it was listed in the documentation accompanying the referral.

[b] See Appendix Q and R for the full list with further breakdown of the sections "Previous diagnosis of JHS or EDS", "Genetic testing for CTD/EDS", and "Family history".

VI. Aim #4: Analyze whether there are factors associated with the referrals that could help predict the appropriateness of the referral

Various factors were assessed to see if they could be predictors of referral appropriateness.

Table 17: Assessment of factors for association with appropriate referrals

	Referral classification (N=143)				
	Appropriate N (%)	**Others[a] N (%)**	**Total N (%)**	**χ^2 (df)**	**p-value[b]**
Sex assigned at birth				**0.024 (1)**	**0.88**
Female	51	74	125 (87.4)		
Male	7	11	18 (12.6)		
Total	58 (40.6)	85 (59.4)	143 (100.0)		
Referral priority				**3.60 (1)**	**0.06**
Routine	48	79	127 (88.8)		
Stat/urgent/emergency	10	6	16 (11.2)		
Total	58 (40.6)	85 (59.4)	143 (100.0)		
Referral source				**1.45 (1)**	**0.23**
Internal	27	31	58 (40.6)		
External	31	54	85 (59.4)		
Total	58 (40.6)	85 (59.4)	143 (100.0)		
Referring provider specialty				**2.27 (1)**	**0.13**
Specialty[c]	40	48	88 (61.5)		
Primary care[c]	18	37	55 (38.5)		
Total	58 (40.6)	85 (59.4)	143 (100.0)		

Insurance (federal vs. commercial)				**0.012 (1)**	**0.91**
Federal[d]	22	33	55 (38.5)		
Commercial[d]	36	52	88 (61.5)		
Total	58 (40.6)	85 (59.4)	143 (100.0)		
Insurance (Auth required vs. no auth required)				**0.12 (1)**	**0.73**
Auth required[d]	29	45	74 (51.7)		
No auth required[d]	29	40	69 (48.3)		
Total	58 (40.6)	85 (59.4)	143 (100.0)		

[a] Other referral classifications include: context-dependent, missing-detail, and inappropriate referrals.
[b] The significance for each statistical test is expressed using a nominal p-value, and no correction has been made for multiple comparisons.
[c] See Appendix M to see the groupings of the referring provider specialties.
[d] See Table 8 to see the groupings of the insurances.

1. *Female vs. male*

There is no difference in the distribution of appropriate referrals between females and males (χ^2 (1) = 0.024, p=0.88; Table 17). There appeared to be a difference between females and males when the appropriateness of the referral was analyzed in four categories, where 33% (N=6) of the referrals for males were context-dependent as opposed to 18% (N=23) for females (Figure 8; Appendix S), however this difference did not reach statistical significance (χ^2 (3) = 3.42, p=0.33).

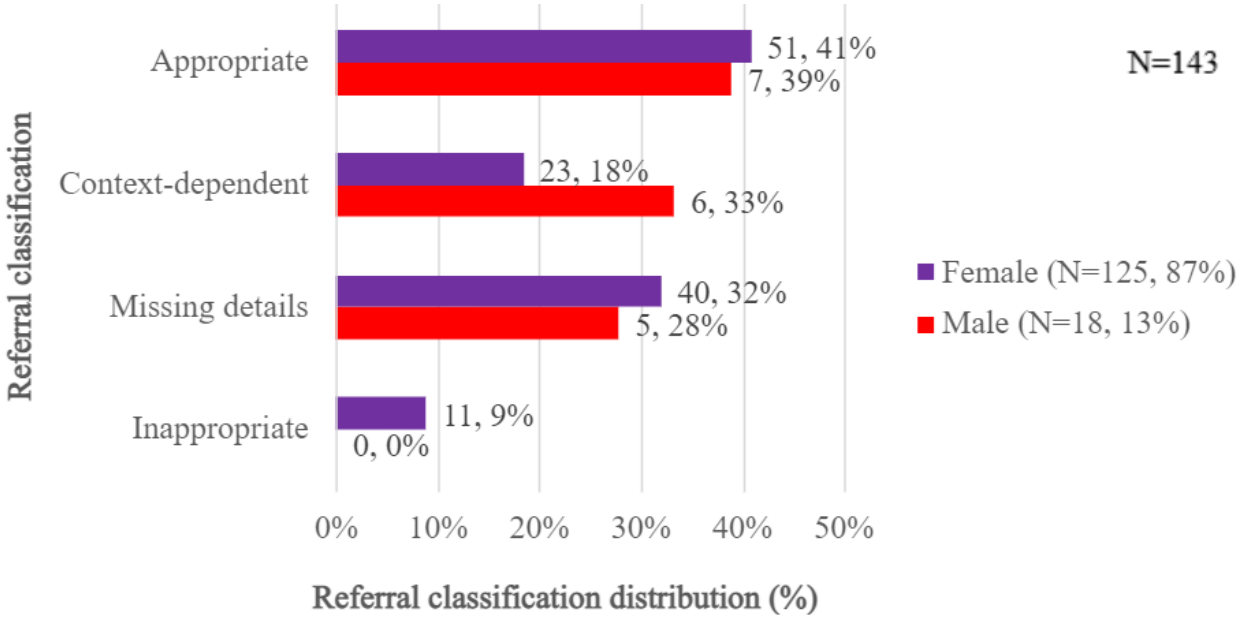

Figure 8: Comparison of referral appropriateness classification distribution between males and females. Referrals for females (N=125, 87%) are represented in purple, and those for males (N=18, 13%) in red. There appeared to be more context-dependent referrals among those for males than those for females, however this difference did not reach statistical significance (χ^2 (3) = 3.42, p=0.33).

2. *Referral priority*

Referrals were divided based on the referral priority: routine vs. not routine (including stat, urgent and emergency) including stat, urgent, and emergency. There was no statistical difference between routine referrals and those with other referral priorities when the referrals were divided into appropriate referrals vs. other referral classifications (context-dependent, missing-details, inappropriate; χ^2 (1) = 3.60, p=0.06; Table 17). However, this finding is suggestive and approaches statistical significance; the majority (N=10, 63%) of referrals with non-routine referral priorities were appropriate referrals, as opposed to only 38% (N=48) of non-routine referrals were appropriate (Figure 9; Appendix S). There appeared to be a difference between routine referrals and those with other referral priorities when the appropriateness of the referral was analyzed in four categories, where 33% (N=42) of the routine referrals were missing

details as opposed to 19% (N=3) of those with other referral priorities (Figure 9; Appendix S), however this difference did not reach statistical significance ($\chi 2$ (3) = 4.47, p=0.22).

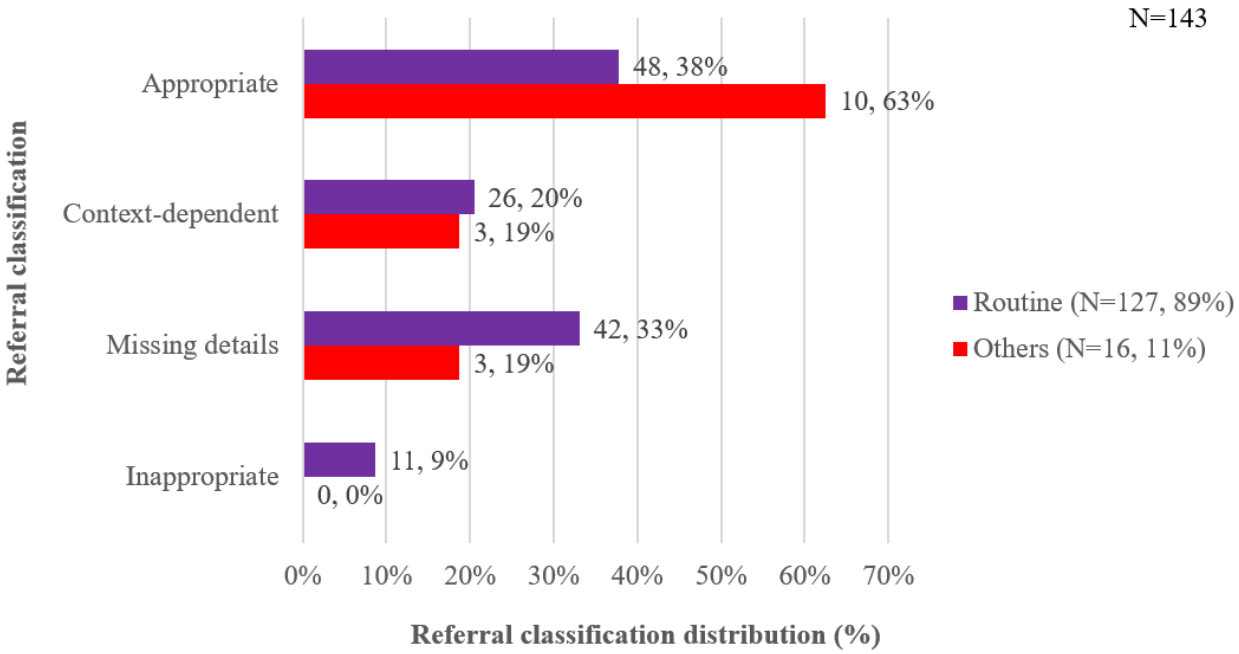

Figure 9: Comparison of referral appropriateness classification distribution within each referral priority. Referrals with routine referral priority (N=127, 89%) are represented in purple, and those with other priorities including stat, urgent, and emergency (N=16, 11%) in red. The majority (N=10, 63%) of referrals with non-routine referral priority are appropriate referrals. There appeared to be fewer appropriate referrals in routine referrals than in non-routine referrals, however this difference did not reach statistical significance ($\chi 2$ (3) = 4.47, p=0.22).

3. *Referral source (internal vs. external) and referring provider specialty*

There was no statistical difference between internal and external referrals when the referrals were divided into appropriate referrals vs. other referral classifications (context-dependent, missing-details, inappropriate) (χ^2 (1) = 1.45, p=0.23; Table 17). Inspection of the distribution across all four categories of appropriateness classification demonstrates that there appear to be fewer (N=12, 21%) referrals that were missing details among internal referrals than those among external referrals (N=33, 39%; Figure 10; Appendix S), however this difference did not reach statistical significance ($\chi 2$ (3) = 5.29, p=0.15).

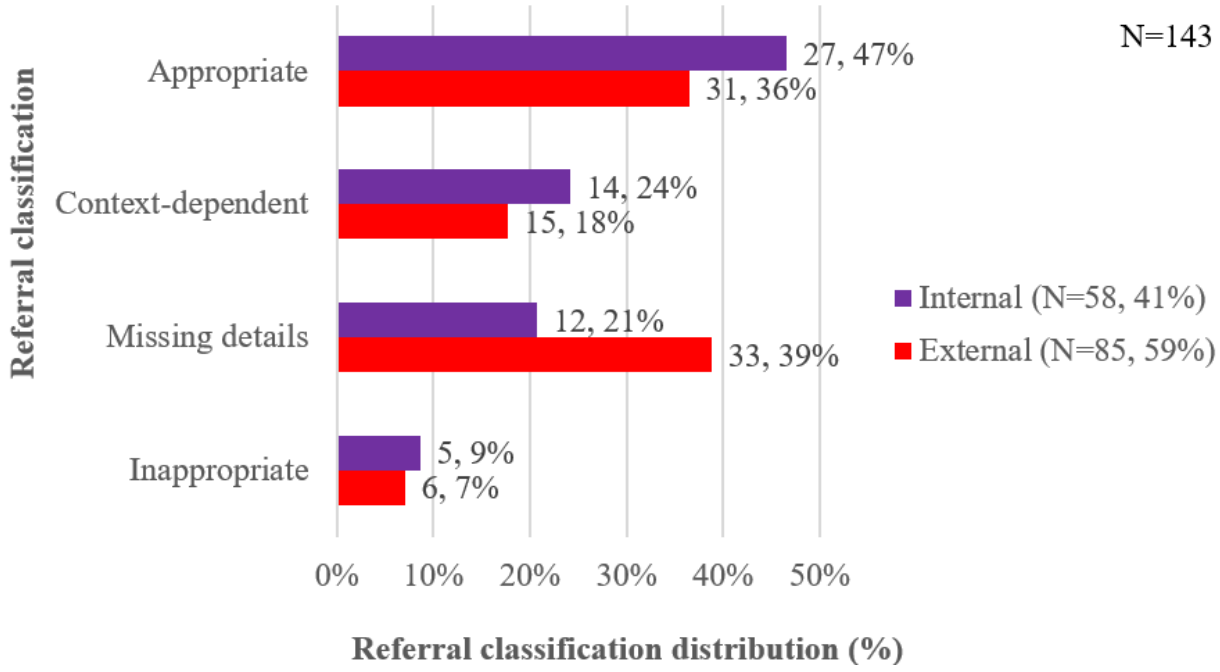

Figure 10: Comparison of referral appropriateness classification distribution within each referral source. Internal referrals (N=58, 41%) are represented in purple and external referrals (N=85, 59%) in red. There appeared to be more referrals missing details among external referrals than among internal referrals, however this difference did not reach statistical significance ($\chi 2$ (3) = 5.29, p=0.15).

The proportion of appropriate referrals was not significantly different between specialty and primary care referrals (χ^2 (1) = 2.27, p=0.13; Table 17). When the percentage distribution of the referral appropriateness classification was calculated within each group, 22% (N=19) of specialty referrals and 47% (N=26) of primary care referrals were missing details (Figure 11; Appendix S). There is a significant difference between specialty referrals and primary care referrals in the distribution across all four categories of appropriateness classification ($\chi 2$ (3) = 10.48, p=0.02).

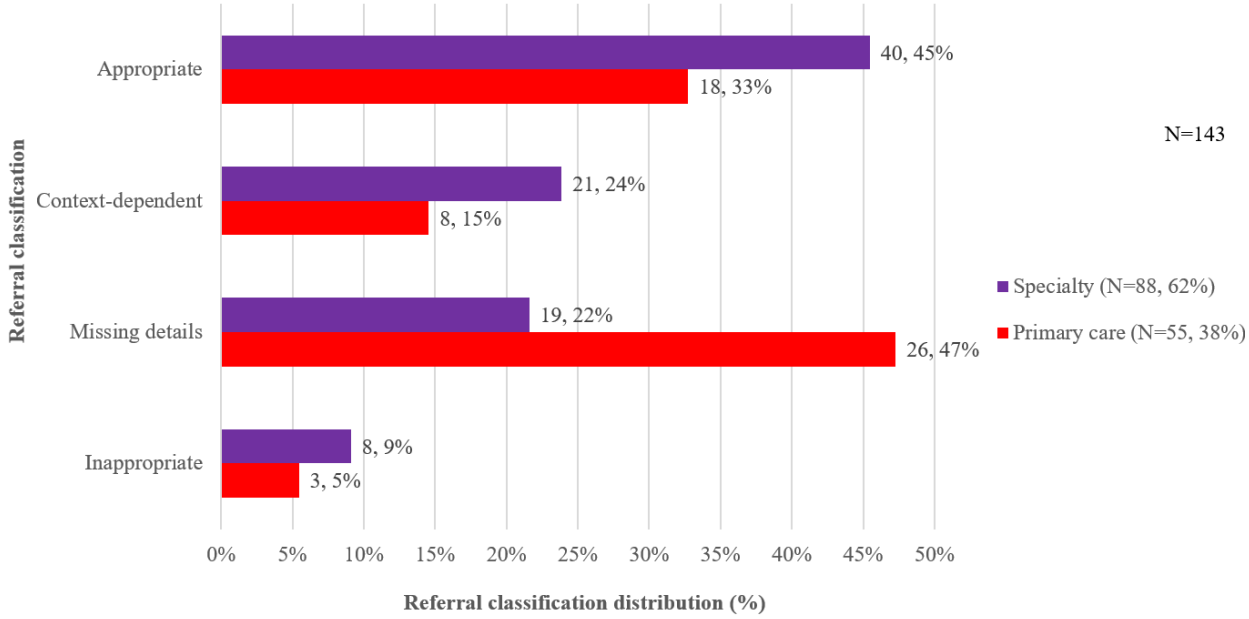

Figure 11: Comparison of referral appropriateness classification distribution within specialty vs. primary care referrals. Specialist referrals (N=88, 62%) are represented in purple and primary care referrals (N=55, 38%) in red. There is a significant difference between specialty referrals and primary care referrals ($\chi 2$ (3) = 10.48, p=0.02).

Figure 12 summarizes the distribution of the referring providers (specialist vs. primary care) for the internal referrals in comparison to external referrals. There is a significant association (χ^2 (1) = 25.09, p<0.0001). The internal referrals were more likely to be from a specialist provider (N=50, 86%); by comparison, only 45% (N=38) of the external referrals were from a specialist provider (Figure 12).

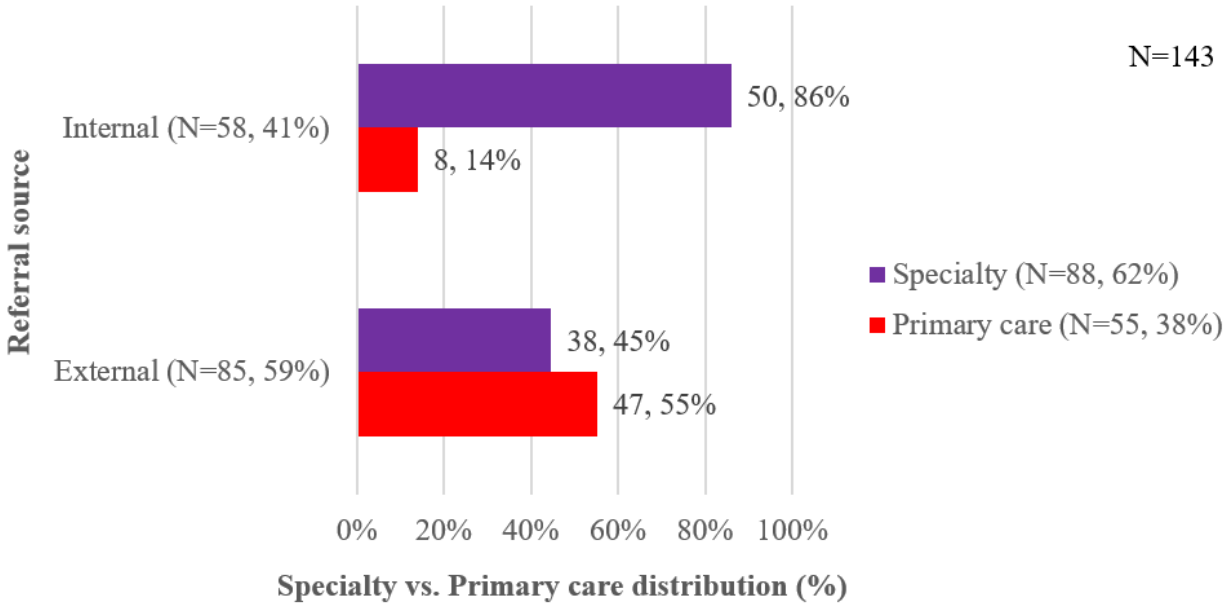

Figure 12: Referral source distribution by specialty vs. primary care referrals. The percentage distribution of specialty (purple) and primary care (red) referrals among each referral source (internal referral of N=58, 41% and external referral N=85, 59%) was calculated. The majority (N=50, 86%) of internal referrals were from specialists. This difference was statistically significant ($\chi 2$ (1) = 25.09, p<0.0001).

4. Insurance

There was no difference in proportions of appropriateness of referrals between those with federal insurance and those with commercial insurance (χ^2 (1) = 0.012, p=0.91; Table 17). Further breakdown of appropriateness classification shows relatively similar distribution, with the seemingly largest difference is that 27% (N=15) referrals with federal insurance context-dependent referrals and 16% (N=14) of the referrals with commercial insurance were context-dependent (Figure 13; Appendix S). In support of this finding, there is not a significant association (χ^2 (3) = 6.18, p=0.10).

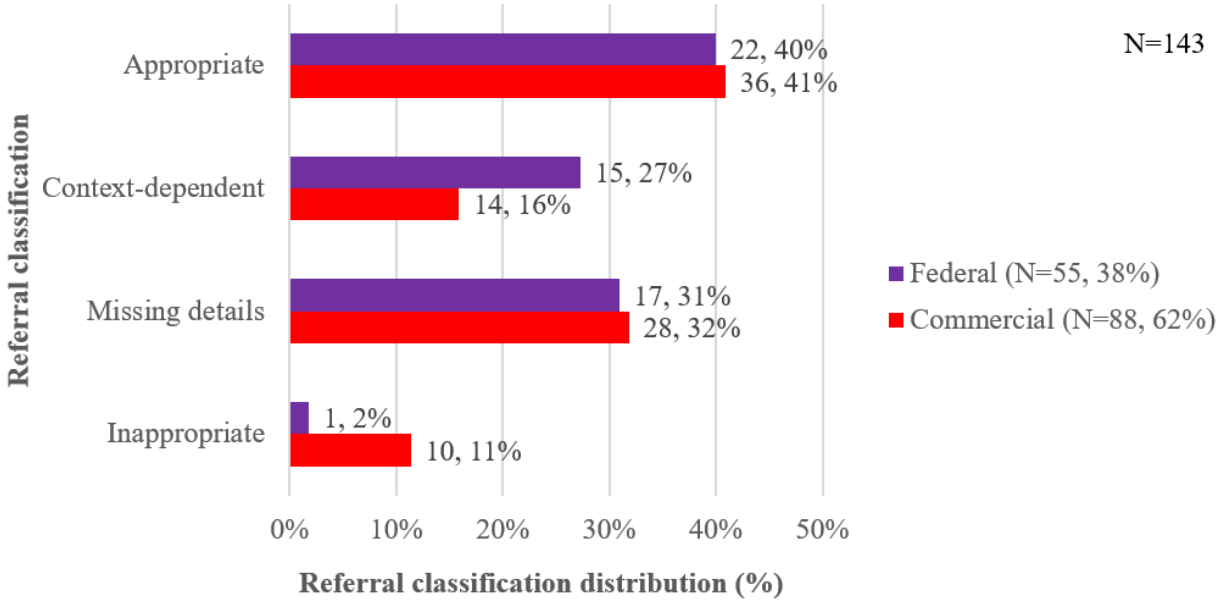

Figure 13: Comparison of referral appropriateness classification distribution within federal vs. commercial insurances. Referrals with federal insurances (N=55, 38%) are represented in purple and those with commercial insurances (N=88, 62%) in red. There were more context-dependent referrals among those with federal insurances than those with commercial insurances, however this difference did not reach statistical significance (χ^2 (3) = 6.18, p=0.10).

There was no difference in proportions of appropriateness of the referral between those with insurance that requires authorization and those with insurance that does not (χ^2 (1) = 0.12, p=0.73; Table 17). The percentage distribution of the referral appropriateness classification appeared to be similar as well and is not statistically significant (χ^2 (3) = 1.63, p=0.65; Figure 14; Appendix S).

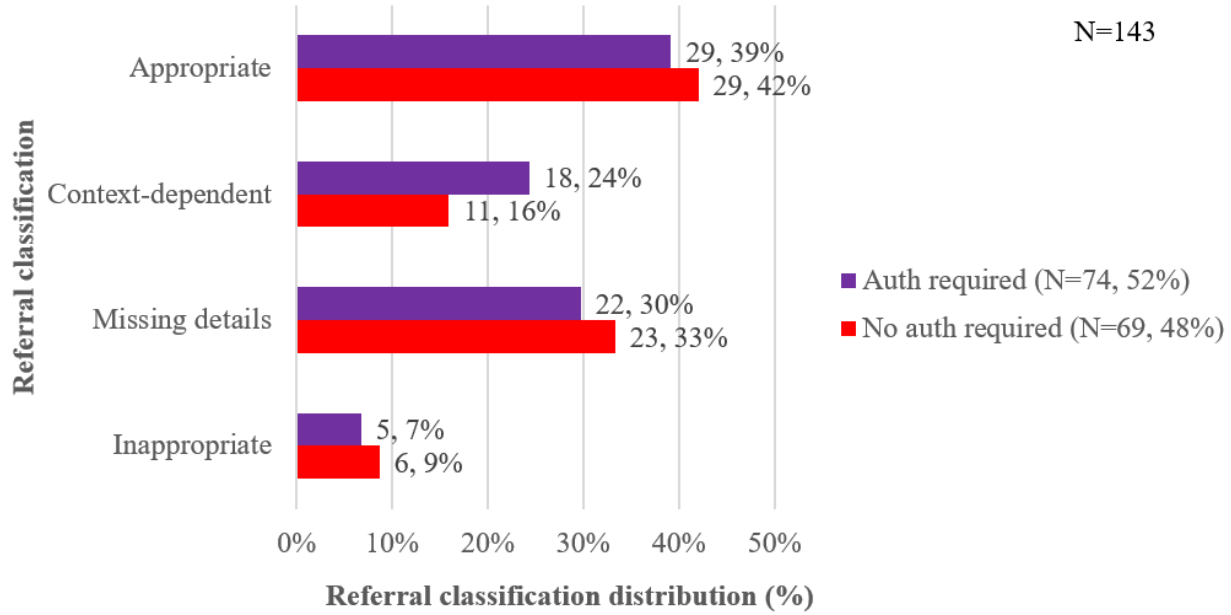

Figure 14: Comparison of referral appropriateness classification distributions within insurances that require authorization vs. those that do not. Referrals with insurance that require authorization (N=74, 52%) are represented in purple, and those with insurance that does not require authorization (N=69, 48%) in red. There appeared to be similarities between referrals with insurance that require authorization and those that do not, which is supported by the finding that it is not statistically significant (χ^2 (3) = 1.63, p=0.65).

Figure 15 summarizes the distribution of referrals with insurance that requires authorization and those with insurance that does not require authorization for the referrals with federal insurance in comparison to those with commercial insurance. There is a significant association (χ^2 (1) = 49.91, p < 0.001). The referrals with federal insurance were more likely to require authorization (N=49, 89%); by comparison, only 28% (N=25) of the commercial referrals required authorization (Figure 15).

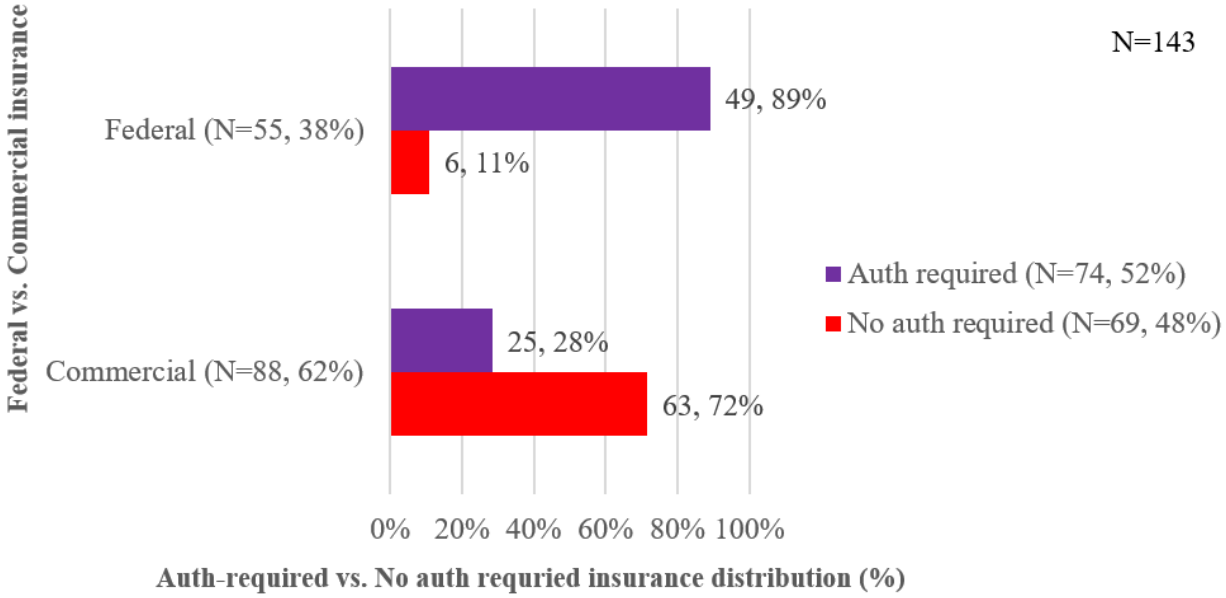

Figure 15: Distribution of referral classifications that requires authorization vs. those that do not by federal vs. commercial insurances. The percentage distribution of referrals with authorization-requiring insurance (purple) and those with insurance that does not require authorization (red) among patients with federal insurance (N=55) and those with commercial insurance (N=88) was calculated. The majority (N=49, 89%) of referrals with federal insurance required authorization, and the majority (N=63, 72%) of referrals with commercial insurance did not require authorization. This difference was statistically significant (χ^2 (1) = 49.91, p<0.001).

5. *ICD-10 codes*

The distribution of the referral appropriateness was assessed within each categorical group of ICD-10 codes (CTD, CTD-related features, possibly CTD/EDS-related features, features commonly associated with hEDS, nonspecific features, and unrelated to hEDS; Appendix T). Groupings "nonspecific features" and "unrelated to hEDS" were omitted from further analysis. The distribution of referral classification appropriateness differed for the referrals which included an ICD-10 code for one of the CTD features compared with those that did not (χ^2 (3) = 16.61, p<0.001). The majority (N=30, 61%) of the referrals with ICD-10 codes under the "CTD features" category were appropriate (Figure 16). The patterns of distribution of referral appropriateness classification were similar across the remaining three categories

("CTD", "Possibly CTD/EDS-related features", "features commonly associated with hEDS"); approximately 40% were appropriate, 20% context dependent, 20-40% missing details, and up to 10% inappropriate (Figure 16; Appendices T-V).

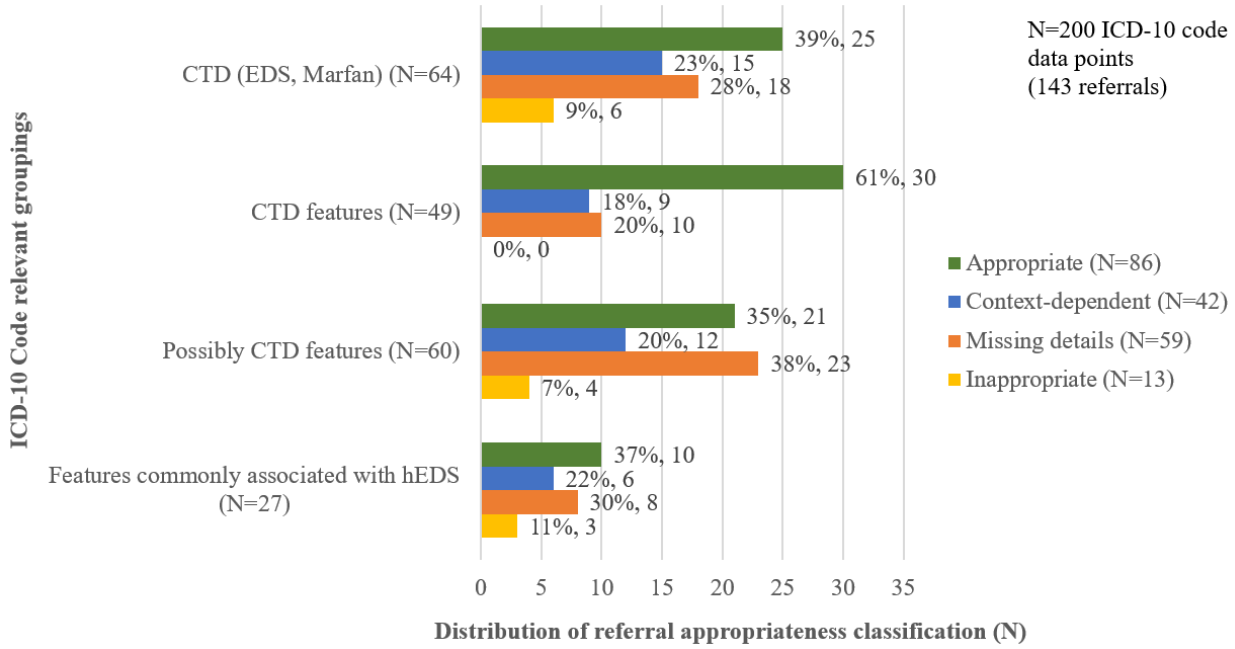

Figure 16: Distribution of referral classification appropriateness within each group of relevant ICD-10 codes. The distribution of the referral appropriateness was calculated within each categorical grouping of ICD-10 codes. Appropriate referrals are represented in green, context-dependent referrals in blue, referrals missing details in orange, and inappropriate referrals in yellow. Groupings of ICD-10 codes that were "nonspecific features" and "unrelated to hEDS" were omitted. The distribution of referral classification appropriateness differed for the referrals which included an ICD-10 code for one of the CTD features, in comparison with those that did not (χ^2 (3) = 16.61, p<0.001).

DISCUSSION

Hypermobile EDS (hEDS) is a complex condition. Individuals with hEDS can have a range of clinical features, and the spectrum of severity can vary for joint hypermobility (JH) and for other heterogeneous clinical manifestations and commonly associated features (Castori et al.,

2017; Gensemer et al., 2021). Unlike other hereditary connective tissue disorders (hereditary CTD), hEDS does not have a molecular confirmatory test, making the diagnostic process longer and difficult due to the procedure for a diagnosis of exclusion (Malfait et al., 2017). As noted in the diagnostic criteria developed by The International Ehlers-Danlos syndrome Consortium, other conditions must be excluded before making a clinical diagnosis of hEDS (Malfait et al., 2017). The hEDS diagnostic process may involve evaluations by various specialties to rule out other possible explanations for features seen in the patient. For example, individuals with JH and/or pain should have a rheumatological examination, and those with easy bruising or bleeding may be referred to hematology to rule out common inherited bleeding disorders (Aletaha et al., 2010; Smolen et al., 2016; Ballas & Kraut, 2008). These elimination steps are crucial to ensure that patients are not incorrectly diagnosed with hEDS, a disorder that only has symptomatic treatment, if they have a condition that has a disease-specific treatment available. However, some providers may be referring patients to genetics first when their patients have features that the providers associate with hEDS rather than considering other referrals that may be more appropriate (such as to rheumatology or hematology). Educating referring healthcare providers may be one way of streamlining the hEDS diagnostic journey.

A 2019 study found that patients with suspected Ehlers-Danlos syndrome (EDS)/CTD benefit from evaluation in a medical genetics clinic (Ihinger, 2019). However, there appears to be more patients than current appointment availability in medical genetics clinics. Because of the abundant referrals for possible hEDS, the triaging process is difficult. For example, although some indications, such as possible vascular EDS (vEDS), require urgent attention due to life-threatening features, these referrals may be delayed by being grouped with other hEDS or CTD referrals that a medical genetics service may receive more frequently and abundantly.

To improve this situation, it may be helpful to provide guidance to other medical providers regarding "diagnostic processes" for individuals with suspected hEDS or other CTD that may improve the kind and quality of information provided with the referral. This may ultimately help providers to make more specific and targeted referrals and also help patients to have a clearer pathway for their medical journey. As a first step to creating such guidelines, this study aimed to understand what the referring providers document in their referrals and why they refer patients for genetic evaluation.

I. Difficulty of triaging hEDS/CTD referrals

First, the appropriateness of each referral was assessed to recognize how many referrals are currently considered to be appropriate. To consistently classify the appropriateness of each referral, a classification scheme was developed through a consensus process of regenerating and redefining levels of appropriateness. The base of the classification was built by first incorporating diagnostic criteria for hEDS and then evolved by including features seen in other CTD. The development of the classification flowchart required discussion among the research team and an iterative process of applying the classification scheme under development to the 143 referrals analyzed. Despite the created flowchart shown in Appendix A, reviewing records associated with a referral and classifying the appropriateness of each referral took about 30 minutes to an hour, with additional time needed when the data had to be revisited or reclassified each time a revision was made to the classification scheme (data not included). This may be a reflection of how time-consuming it can be to review referral documentation for suspected hEDS and how difficult it can be to triage cases for hEDS/CTD when information is not provided

adequately. In addition, it indicates that having a flowchart is vital for triaging referrals more consistently.

II. (Lack of) documentation in current referrals to genetics for hEDS/CTD

Knowing the details of features that a patient has and does not have is vital in clinical genetics evaluations. As a part of considering differential diagnoses along with hEDS, certain features are valuable to assess. The presence or absence of the CTD-related features leads to increasing or decreasing suspicion that the patient has hEDS or another CTD and affects the urgency with which a patient was scheduled in the genetics clinic, or recommended to have other follow-up (Colombi et al., 2015, Malfait et al., 2017). However, such details on features were often not provided, resulting in 51% (N=74) of the referrals left under context-dependent or missing-details categories.

A major feature of hEDS that was often lacking in details in the referring documentation was JH. Having generalized joint hypermobility (GJH) is a major diagnostic criterion for hEDS (Malfait et al., 2017). If a patient has JH, the information about how many joints or which joints are involved would be essential. However, 38% (N=28) of the referrals with reported JH did not assess where the JH was seen or which joints were hypermobile (Table 15). In addition, GJH is evaluated using the Beighton scale, and individuals must meet the age- and sex-related cutoff score in order to be classified as having GJH (Malfait et al., 2017). It is valuable to know whether someone met the Beighton criteria because there are CTD that do not include GJH among the features (Colombi et al., 2015, Malfait et al., 2017). However, only 25 referrals (34% of referrals that documented JH in the clinical notes) reported Beighton scores (Table 15). One possible reason for this finding is that many providers may not have been aware of the Beighton test or trained in how to perform it. Educating healthcare providers on the importance of the

Beighton scale and how to use it may improve the number of referrals with reported Beighton scores.

Other CTD-related features may also aid in considering differentials, meaning that asking about the presence of other CTD-related features is also crucial. However, features of EDS that do not involve joints, easy bruising and elastic skin were less commonly reported in this sample (N=25, 18% and N=13, 9% respectively). In fact, more than 75% (N=110) of the referrals did not document the presence or absence of CTD-related features including easy bruising and elastic skin (Figure 7). This finding is consistent with a previous study (Ihinger, 2019) and may be due to there being many features related to CTD that may be less well-known than JH and that are not evaluated. A list of CTD-related features should be provided to physicians who may evaluate individuals with suspected CTD to guide them on what to assess in a patient with suspected hEDS/CTD.

Upon gauging the common referral indications, it was also noted that the EDS subtype that a provider suspected or that a patient thought they had was often not specified. The majority (53%, N=18) of referrals for genetic testing were for nonspecific “EDS”. Two patients (1%) were also referred for previous diagnoses of EDS, but the subtypes that had been diagnosed were not included. Specifying which subtype was previously diagnosed or suspected may help during the genetic clinic’s triaging process, especially if the patient has a condition or EDS subtype such as vEDS, where they may be at risk for life-threatening complications and need an urgent evaluation by genetics (Malfait et al., 2017). If the subtype is unclear or unspecified, there may be an undesirable delay in scheduling the patient. Regardless of the condition, the genetics clinic will be able to triage patients more efficiently if the suspected subtypes of EDS are specified and if any previous genetic test reports are shared with the clinic prior to the appointment.

When there is a lack of information or documentation in the referral, the genetics providers must request the information from the referring provider and other providers or from the patient to determine if and how soon the patient should be scheduled for the genetics evaluation. As Ihinger (2019) discussed, genetics providers require as much information regarding the patient's features as possible to narrow down differential diagnoses and to consider appropriate next steps, such as referring the patient to another specialist, ordering an imaging study, or ordering genetic testing. In order to help providers to improve their referrals, having a list of CTD-related features that they can document as present or absence may be beneficial, since there are many features to consider when thinking about CTD.

III. Captured referring providers' understanding and misunderstanding of hEDS

Recognizing what is understood or misunderstood by referring providers is helpful when constructing educational materials to promote appropriate referrals. Although this study did not include a formal qualitative analysis, illustrative quotes/statements from the referral documentation are presented to help elucidate referring providers' understanding of hEDS. Some providers demonstrated in their clinic notes good understanding of JHS and hEDS. For example, one provider listed educational materials regarding both hereditary and acquired JH in the patient's medical record. The documentation provided a good introduction to hypermobility syndromes and mentioned that laboratory tests are not available for every hypermobility syndrome and that hEDS is a diagnosis of exclusion that can only be diagnosed clinically (Malfait et al., 2017). The inclusion of credible educational material may have been informative and beneficial not only for the patient but also for other physicians.

Another provider demonstrated a strong understanding of the presence and absence of features in each of the more common EDS subtypes by documenting, "The vascular subtype of EDS does not usually result in significant joint hypermobility which is why I [the referring provider] did not think you [the patient] had this subtype." On the other hand, one provider stated incorrectly that joint dislocations are only seen in classical EDS (cEDS) and not in hEDS. This illustrates the potential benefit of having a list of features that can help the provider know whom to refer and also simplify triage for the genetics clinic.

Certain evaluations are helpful to complete before a genetics evaluation for hEDS because they are included among the guidelines for evaluation for hEDS. For example, an echocardiogram is needed to evaluate for aortic root dilation and valvular disease, and ophthalmologic examination can evaluate for ectopia lentis and other eye findings associated with certain hereditary CTD (Colombi et al., 2015). One referring provider suggested that an echocardiogram should be considered after having a medical genetics evaluation. However, the echocardiogram is helpful in making a clinical diagnosis of CTD (Malfait et al., 2017). Having the information ahead of time allows not only for a more efficient genetics evaluation of the patient but also for identification of cases with findings associated with life-threatening conditions that may need a genetics evaluation urgently.

In addition to these evaluations, rheumatological conditions should be excluded as much as possible for non-specific features that are commonly associated with hEDS such as joint pain, abdominal pain, fatigue, and headache (Gensemer et al., 2021, Malfait et al., 2017). These symptoms are not among the hEDS diagnostic criteria and, therefore, cannot be used to diagnose hEDS. Unless they have JH and/or other CTD-related features, it is not likely that patients with such symptoms have hEDS.

Another potential area of misunderstanding was the availability of genetic testing for hEDS. A provider documented that a patient reported having an hEDS diagnosis that had been confirmed by genetic testing, even though currently there is no molecular testing available for hEDS (Malfait et al., 2017). It is unlikely that the patient had genetic testing that "confirmed" hEDS; molecular testing can only exclude other CTD and therefore leave patients with hEDS as a diagnosis of exclusion. It may be that the statement about receiving confirmatory genetic testing was true and that testing had revealed another EDS subtype. A different provider noted that a patient completed genetic testing and was diagnosed with EDS without specifying a subtype. When patients report previous genetic testing, genetics clinics would greatly benefit by having the genetic test report. From the report, genetics providers can evaluate which genes were tested and which were confirmed to have or not have health-altering variants. This way, the genetics team can plan what the appropriate next steps are, whether that be providing personalized risk assessment based on the test result, ordering imaging or other genetic tests, referring to other specialists for further evaluation or management, or identifying possible implications for other family members.

Because of the number of EDS subtypes and their broad spectrum of features, both overlapping and unique, patients may feel overwhelmed when they find EDS upon researching possible diagnoses that could explain their own symptoms. The experience of patients referred for suspected hEDS/EDS was reflected in some of the referral documentation that was reviewed during this study. A patient reported being concerned about having EDS based on researching the internet. These general discussions may list all possible features as if EDS were a singular disorder, then which a patient may assume, for example, that everyone with JH is also at risk for the life-threatening features of vEDS, such as hollow organ or large vessel rupture (Malfait et al.,

2017). This can confuse patients and induce unwanted anxiety and stress. If providers were to have educational materials or a protocol regarding referrals for EDS, they may be able to explain that there are different EDS subtypes and which may be more or less likely based on features that are present or absent in the patient. This may allow patients to feel relieved to know what conditions were or were not being considered, ultimately alleviating patient stress.

Studies report that some patients with symptoms such as chronic pain and/or fatigue feel dismissed by their healthcare providers, including patients with EDS (McManimen et al., 2019; Halverson et al., 2021; Merone et al., 2022). A clinical note in our study documented a patient reporting to have felt dismissed by providers. When patients have features commonly associated with hEDS, like chronic, widespread joint pain and muscle aches, being aware of disorders such as hEDS that can cause joint pain without evidence of inflammation and examining the patient for JH will not only help patients feel heard but also lead them to the appropriate diagnostic evaluation.

Because some degree of JH is not rare in the general population (Anderson & Lane, 2022), better education for providers regarding which additional features should be looked for that would suggest a diagnosis of EDS will help make more appropriate referrals and prevent unnecessary referrals to genetics.

IV. Identification of groups of providers who may benefit from hEDS/CTD education

This study also looked at specialties that refer patients to genetics for hEDS/CTD. Of the referrals, 39% (N=55) were from rheumatology, 27% (N=38) from family medicine, and 11% (N=16) from internal medicine (Figure 5). This finding was similar to the result in a previous research study that looked at referring providers' specialties for patients who were seen for

genetics evaluation of suspected EDS/CTD in one adult genetics clinic from January 2014 to March 2019. In that study, the top two specialties were general practice (N=54, 36%) and rheumatology (N=47, 31%) (Ihinger, 2019). This information will be helpful in thinking about which specialties may benefit from receiving hEDS/CTD education and what the focus should be when developing educational materials for them.

Several factors were analyzed to see if they could be predictors of appropriate referrals. These included sex assigned at birth, referral priority, referral source, referring provider specialty, and insurance types. None of these were statistically significant regarding referral appropriateness when it was classified into two groups: appropriate vs. other classification categories combined (Table 17). However, certain patterns were observed when the distribution across all four appropriateness categories was analyzed. The distribution of appropriateness categories was significantly different between referrals from specialist providers and those from primary care providers (χ^2 (3) = 10.48, p=0.02; Figure 11). Primary care referrals were more likely to be missing relevant details than the referrals from specialists (Figure 11). One possible explanation is that primary care providers may have a shorter appointment time with each patient than the specialists, resulting in limited time to ask necessary follow-up questions. However, the time each provider spent with their patients was not analyzed in this study.

Referrals with priority listed as routine appeared less likely to be categorized as appropriate than referrals with other priorities, such as stat, urgent, and emergency, although this difference was not statistically significant (χ2 (3) = 4.47, p=0.22; Figure 9). This observation is not surprising, since non-routine referrals may be more likely to list features that the providers find concerning. Internal referrals appeared to include more pertinent details than external referrals (Figure 10). This could be because external physicians may lack access to a genetics

expert/clinic, thus communicating less frequently with the genetics clinic than internal physicians.

It is interesting to note from the analysis of the ICD-10 codes accompanying the referrals that the group of providers who included at least one ICD-10 code for a feature directly related to the hEDS diagnostic criteria had the highest proportion of appropriate referrals (Figure 16). This may indicate that education for other providers regarding incorporating these features into their referral documentation may increase appropriate referrals.

In summary, these findings are useful when considering which providers should be included in the educational outreach for hEDS/CTD. They also suggest opportunities for strategies to help referring providers make more appropriate referrals to the medical genetics clinic for evaluation of hEDS and other CTDs.

V. Study limitations and future directions

One study limitation is that about half (N=79, 55%) of the individuals who were referred resided in Orange County, where UCIMC is located, either at the time of the referral or at the time of data collection (Table 9; Figure 4). Moreover, 97% (N=138) of the referrals were for patients who resided in Southern California (Table 9; Figure 4). The findings may not be generalizable to other regions; a larger study that encompasses referrals for patients from other areas of the country will be necessary to understand whether the findings in this study are generalizable to other clinics and to other parts of the country.

Similarly, this study attempted to evaluate as many types of hEDS referrals as possible by including various ICD-9/ICD-10 codes that are commonly associated with hEDS. However, because of such specific criteria, this study may not have captured all referrals to the genetics

clinic for a reason related to hEDS/CTD. In future studies, the samples should be randomly selected from a larger pool of referrals.

This chart review research also collected referring providers' documentation. Two major limitations arise from this: (1) Only clinical documentation that led up to the referral was reviewed for this study, meaning that there may be other features or thoughts associated with hEDS that referring providers documented in other clinical notes but not in the record that was used for data collection. (2) Similarly, for external referrals, the only available documents were those that were sent to the clinic, and therefore there may be missing information that was not captured in this study. If the referring providers have documented additional relevant detail in records that were not sent together with the referral, it will be important to provide them with additional instruction regarding which documentation to send. Alternatively, it may be that some referring providers would benefit from receiving additional education on how best to collect and document information that could then be sent together with a referral to the genetics clinic for evaluation for hEDS/CTD.

One outcome of this study is the creation of a flowchart to consistently classify the appropriateness of the referrals. Although most referrals could be classified using the flowchart, some referrals had to be discussed with the research team to determine their appropriateness based on additional features/indications that were not specifically included in the flowchart. For these referrals, a case-by-case approach attempted to ensure that the referrals were not wrongfully categorized as inappropriate or lacking in details. The additional criteria that were used to classify these referrals were then incorporated into the classification flowchart and checked against the remaining referrals, in an iterative process. The classification scheme that

was developed in this study could be tested in different settings and be tested against the outcome of the eventual genetics evaluation.

This study may be expanded upon by collecting other details from the referring providers' documentation, including studies/tests done prior to the genetics evaluation but not included in the referring documentation, such as echocardiograms, other consultations such as physical therapy or orthopedics, and the results. The consistency and efficacy of the triaging process using the flowchart should also be evaluated. Future research could track the outcome of the referrals that were classified as appropriate to validate the classification scheme. Lastly, developing and evaluating educational material for better hEDS/CTD referral guidance or questionnaires for referring providers/patients to fill out before hEDS/CTD referral would be a valuable next step to streamline the medical journey for individuals with suspected hEDS and to improve the referral quality. Testing the educational material/questionnaire and seeing if they improve the referral content may be an important focus of a future study.

VI. Conclusions

This study aimed to understand why medical professionals refer patients for genetic evaluation for hEDS and what they document in the referral documentation. While research continues to better understand the clinical features and etiology of hEDS, genetics clinics are currently overwhelmed by referrals for hEDS and other CTD. Through exploring hEDS/CTD referral factors and contents, this study resulted in findings that will contribute to improve the flow of diagnostic journey for individuals with suspected hEDS.

The research study created a classification scheme to identify appropriate referrals for hEDS/CTD, which was then developed into a flowchart to classify the appropriateness

consistently. This flowchart considered categorizations of referrals for patients with varying features related to and/or associated with CTD by incorporating the current hEDS diagnostic criteria as well as features seen in other CTD. This study also identified specialties that frequently referred to genetics for hEDS as well as common shortcomings of the referrals that did not get classified as appropriate, where many CTD related features were either not assessed or documented. This study did not find any referral factors to be statistically significant regarding referral appropriateness between appropriate referrals and referrals with other classification categories combined. However, when the distribution across all four appropriateness categories was analyzed, primary care referrals vs. specialty referrals was identified as a possible predictor for those missing details. These findings identified a group of referrals where there are opportunities to be improved.

This study may be the foundation of future directions to provide education to other physicians that may frequently care for patients with suspected hEDS/CTD. These findings may contribute to an improved referral protocol for providers, improved appropriateness of referrals to genetics, reduction of patient wait time, and prompt scheduling of patients with increased risk of serious complications, all of which would allow genetics clinics to provide better support to patients and providers.

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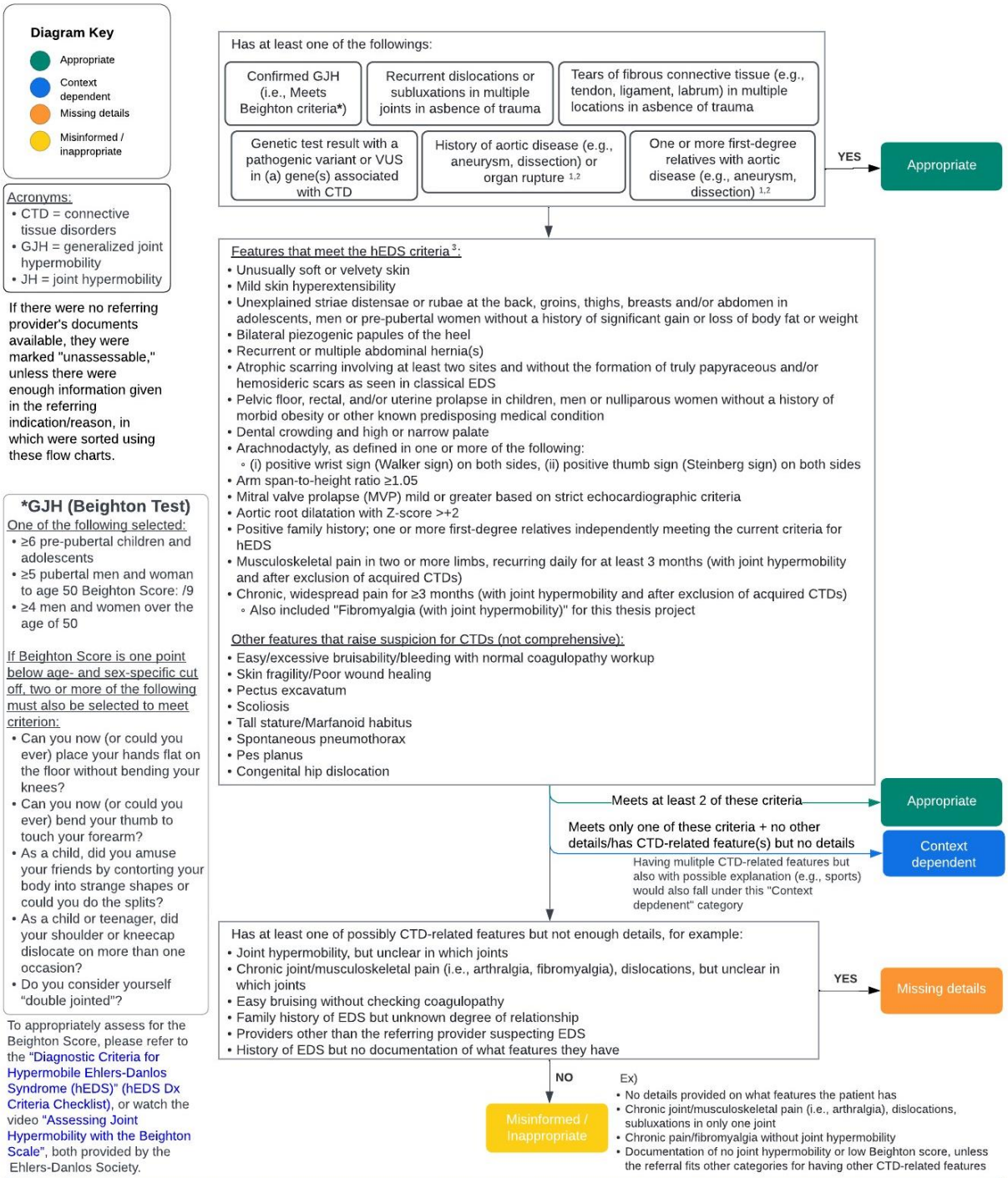
APPENDIX A

Flowchart for consistent classification of referral appropriateness



1 Erwin, I. J. P., null, null, Cibotti, -Sun Morgane, & Elma, M. (2022). 2022 Aortic Disease Guideline-at-a-Glance. Journal of the American College of Cardiology, 80(24), 2348–2352. https://doi.org/10.1016/j.jacc.2022.10.001

2 Isselbacher, E. M., Preventza, O., Hamilton Black, J., Augoustides, J. G., Beck, A. W., Bolen, M. A., Braverman, A. C., Bray, B. E., Brown-Zimmerman, M. M., Chen, E. P., Collins, T. J., DeAnda, A., Fanola, C. L., Girardi, L. N., Hicks, C. W., Hui, D. S., Schuyler Jones, W., Kalahasti, V., Kim, K. M., … Woo, Y. J. (2022). 2022 ACC/AHA Guideline for the Diagnosis and Management of Aortic Disease: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. Circulation, 146(24), e334–e482. https://doi.org/10.1161/CIR.0000000000001106

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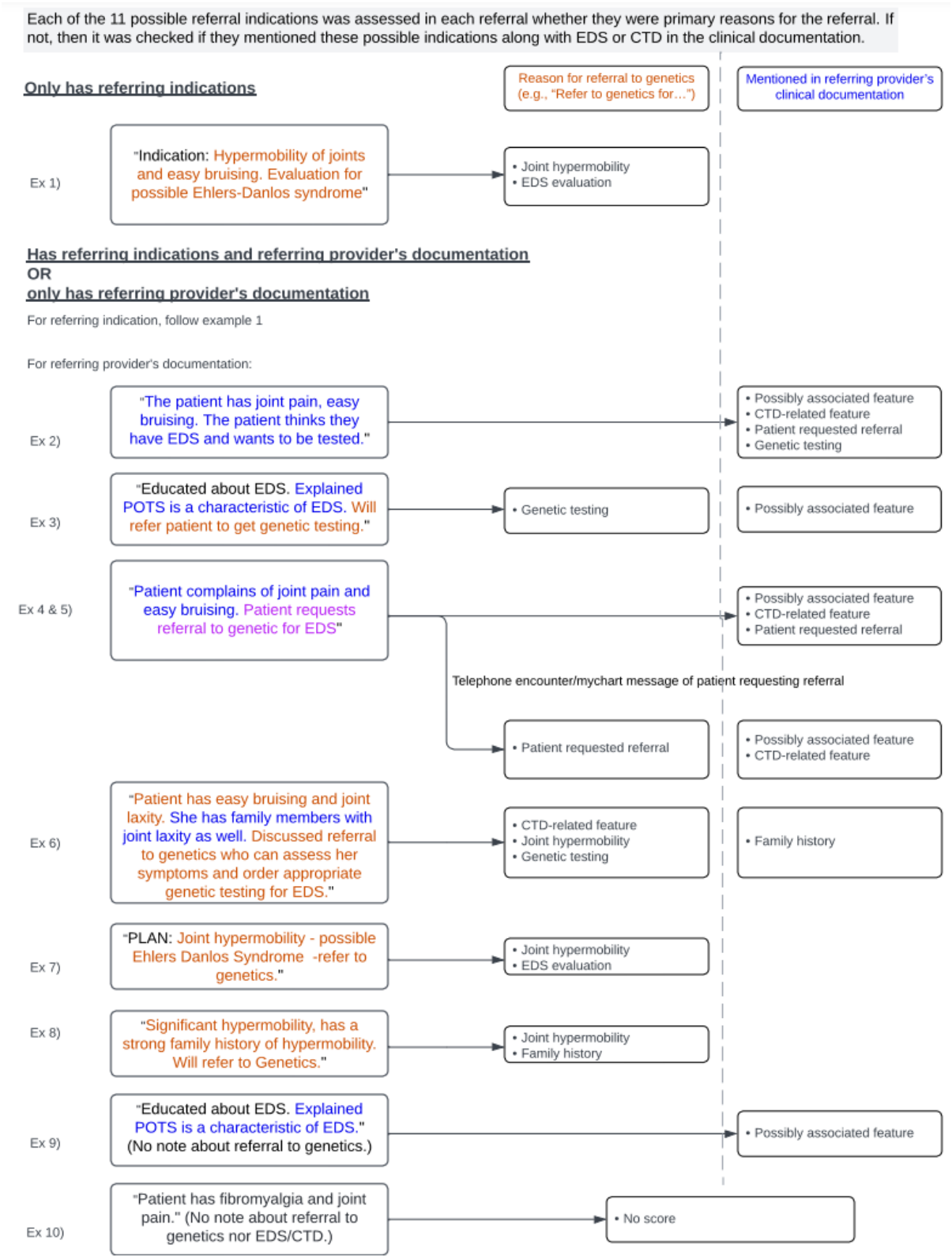
APPENDIX B

Examples of referral indication scoring



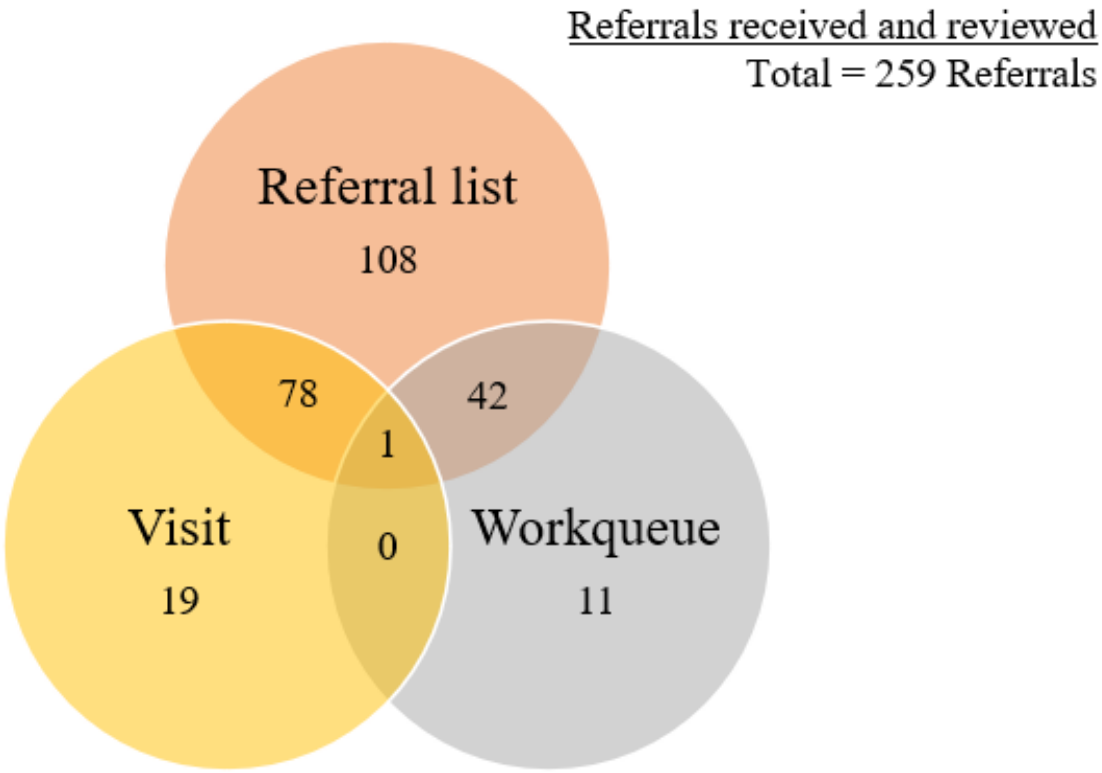
APPENDIX C

Number of referrals included and excluded from each of the three referral sources

	Work queue	Visits	Referral list
Met IRB protocol	49	48	152
Included in data analysis	44	43	135
Referring indication only	3	8	19
Referring provider documentation available	41	35	116
Excluded from data analysis	10	55	94
No referring provider documentation available	5	5	17
Follow-up	0	3	4
Did not meet IRB protocol	5	47	73
Total	54	98	229

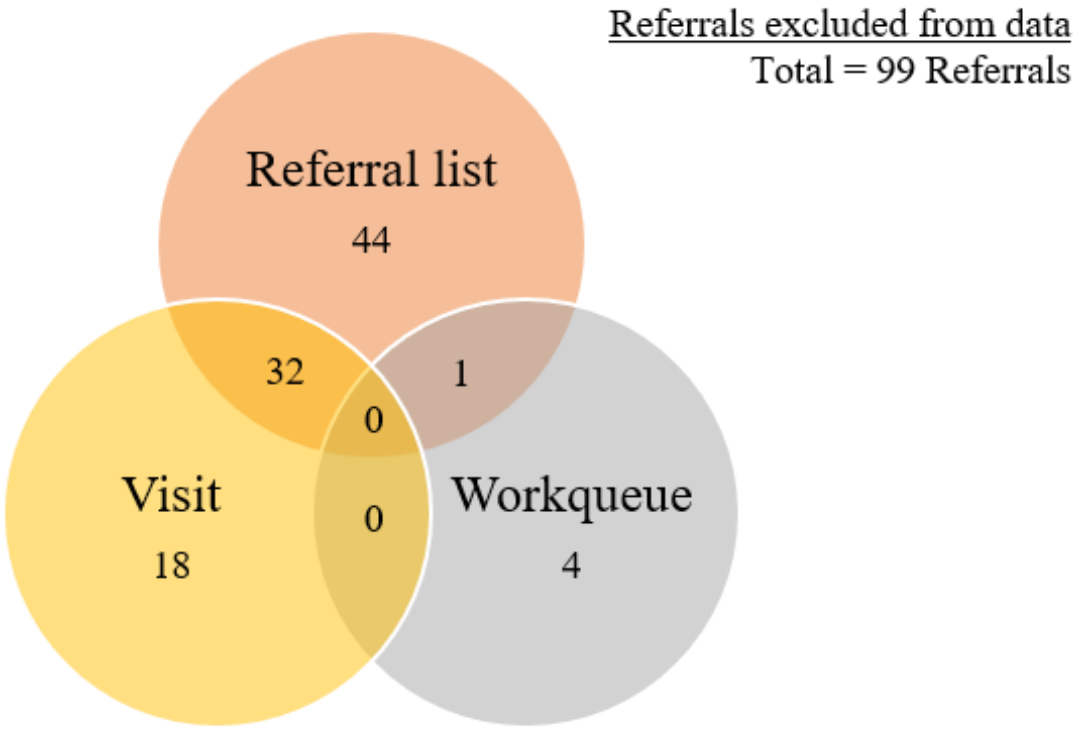
APPENDIX D

Number of referrals received and reviewed distributed by referral sources



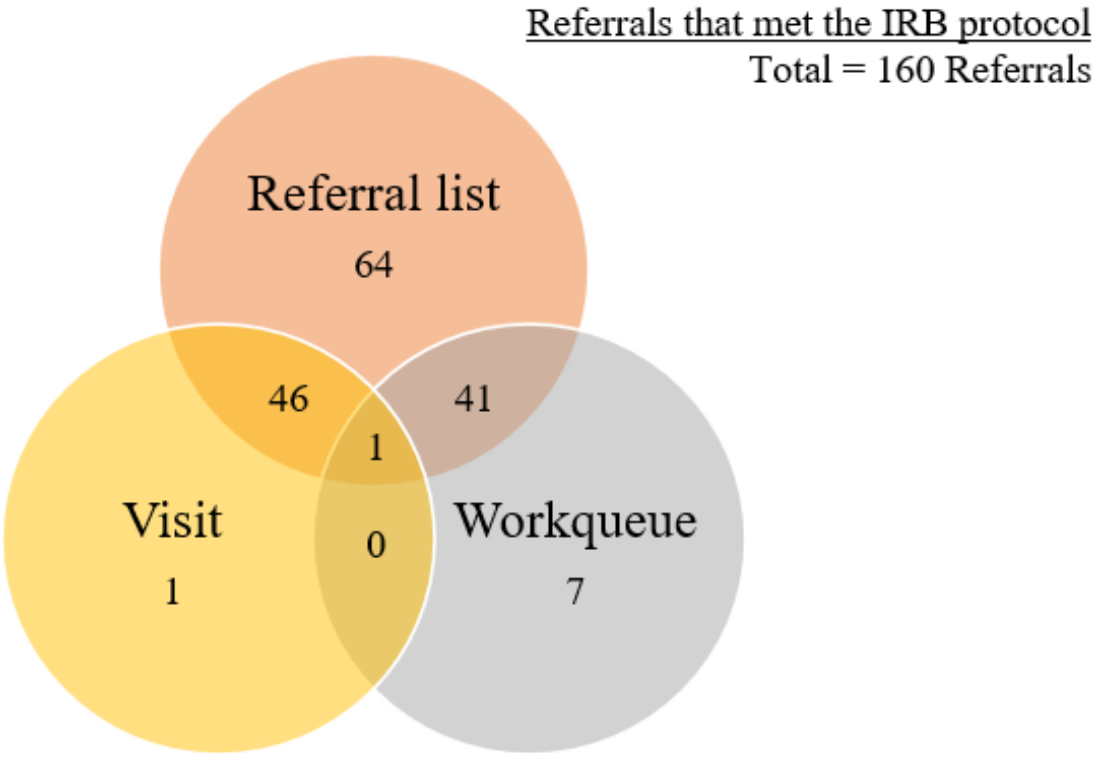
APPENDIX E

Number of referrals excluded from data analyses distributed by referral sources



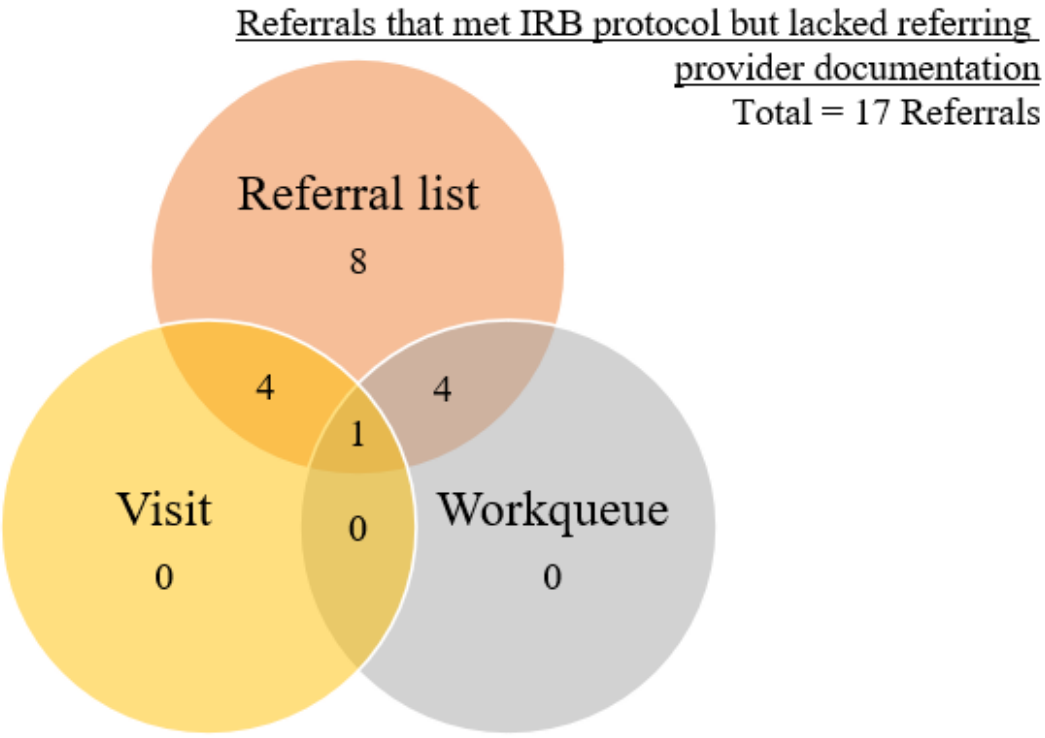
APPENDIX F

Number of referrals that met the IRB protocol distributed by referral sources



APPENDIX G

Number of referrals that met the IRB protocol but lacked referring provider documentation distributed by referral sources



APPENDIX H

Number of hEDS/CTD referrals included in analysis, by year

Year	Referrals w referring provider's notes and/or indications (N=143)	Referrals w/o referring provider's notes or referring indications (N=17)	Total (N = 160)
	N (%)	N (%)	N (%)
Nov-Dec 2017	2 (1.4)	—	2 (1.3)
2018	9 (6.3)	—	9 (5.6)
2019	6 (4.2)	3 (17.6)	9 (5.6)
2020	14 (9.8)	1 (5.9)	15 (9.4)
2021	37 (25.9)	3 (17.6)	40 (25.0)
Jan-Oct 2022	75 (52.4)	10 (58.8)	85 (53.1)

APPENDIX I

Sex assigned at birth and age distribution of referrals included in analysis

	Referrals w referring provider's notes and/or indications (N=143)	Referrals w/o referring provider's notes or referring indications (N=17)	Total (N = 160)
Sex assigned at birth			
Female	125 (87.4)	16 (94.1)	141 (88.1)
Male	18 (12.6)	1 (5.9)	19 (11.9)
Age			
Min-max	18-77	19-71	18-77
Mean/SD	34.3/11.7	36.2/14.2	34.5/12.0
Age groups	N (%)	N (%)	N (%)
18-19	4 (2.8)	1 (5.9)	5 (3.1)
20-29	54 (37.8)	7 (41.2)	61 (38.1)
30-39	46 (32.2)	3 (17.6)	49 (30.6)
40-49	24 (16.8)	4 (23.5)	28 (17.5)
50-59	9 (6.3)	1 (5.9)	10 (6.3)
60-69	5 (3.5)	—	5 (3.1)
70-77	1 (0.7)	1 (5.9)	2 (1.3)

APPENDIX J

Insurance distribution of referrals included in analysis

Insurance		Referrals w referring provider's notes and/or indications (N=143)	Referrals w/o referring provider's notes or referring indications (N=17)	Total (N = 160)
		N (%)	N (%)	N (%)
Commercial	PPO[a]	63 (44.1)	2 (11.8)	65 (40.6)
	HMO	18 (12.6)	7 (41.2)	25 (15.6)
	EPO	3 (2.1)	1 (5.9)	4 (2.5)
	LOA	1 (0.7)	1 (5.9)	2 (1.3)
	HPN	1 (0.7)	—	1 (0.6)
	POS	1 (0.7)	—	1 (0.6)
	TPA	1 (0.7)	—	1 (0.6)
Commercial (Total)		88 (61.5)	11 (64.7)	99 (61.9)
Federal	Medi-Cal	28 (19.6)	4 (23.5)	32 (20.0)
	Medicaid	12 (8.4)	—	12 (7.5)
	Medicare (A&B)	6 (4.2)	1 (5.9)	7 (4.4)
	Medicare (Managed)	3 (2.1)	—	3 (1.9)
	Tricare	6 (4.2)	1 (5.9)	7 (4.4)
Federal (Total)		55 (38.5)	6 (35.3)	61 (38.1)

[a] PPO referrals do not require authorization.

APPENDIX K

Distribution of counties patients resided in at the time of the referral or data collection (for referrals included in analysis)

State	County	Referrals w referring provider's notes and/or indications (N=143)	Referrals w/o referring provider's notes or referring indications (N=17)	Total (N = 160)
		N (%)	N (%)	N (%)
California	Los Angeles	27 (18.9)	6 (35.3)	33 (20.6)
	Marin	1 (0.7)	—	1 (0.6)
	Mendocino	1 (0.7)	—	1 (0.6)
	Orange	79 (55.2)	6 (35.3)	85 (53.1)
	Riverside	12 (8.4)	3 (17.6)	15 (9.4)
	San Bernardino	11 (7.7)	1 (5.9)	12 (7.5)
	San Diego	6 (4.2)	1 (5.9)	7 (4.4)
	San Luis Obispo	1 (0.7)	—	1 (0.6)
	Ventura	2 (1.4)	—	2 (1.3)
California (Total)		140 (97.9)	17 (100.0)	157 (98.1)
Nevada[a]	Clark	1 (0.7)	—	1 (0.6)
Texas[a]	Travis	1 (0.7)	—	1 (0.6)
Washington[a]	King	1 (0.7)	—	1 (0.6)

[a] Referrals of patients' addresses were from outside of CA at the time of the referral or data collection. However, they would have needed to be in CA for their visits.

APPENDIX L

Referral class and priority distribution of referrals included in analysis

	Referrals w referring provider's notes and/or indications (N=143)	Referrals w/o referring provider's notes or referring indications (N=17)	Total (N = 160)
	N (%)	N (%)	N (%)
Referral class			
Internal	58 (40.6)	1 (5.9)	59 (36.9)
External	85 (59.4)	16 (94.1)	101 (63.1)
Referral priority[a]			
Routine	127 (88.8)	16 (94.1)	143 (89.4)
Stat	3 (2.1)	—	3 (1.9)
Urgent	8 (5.6)	1 (5.9)	9 (5.6)
Emergency	5 (3.5)	—	5 (3.1)

[a] The categories are listed in order of increasing priority.

APPENDIX M

Full list of referring provider specialties

Referring provider specialty		Referrals w referring provider's notes and/or indications (N=143)	Referrals w/o referring provider's notes or referring indications (N=17)	Total (N = 160)
		N (%)	N (%)	N (%)
Primary care	Family medicine	38 (26.6)	9 (52.9)	47 (29.4)
	Internal medicine	16 (11.2)	4 (23.5)	20 (12.5)
	Pediatrics	1 (0.7)	—	1 (0.6)
Primary care (Total)		55 (38.5)	13 (76.5)	68 (42.5)
Specialty	Allergy & Immunology	1 (0.7)	—	1 (0.6)
	Cardiology	5 (3.5)	—	5 (3.1)
	Gastroenterology	2 (1.4)	—	2 (1.3)
	Hematology & Oncology	5 (3.5)	—	5 (3.1)
	Internal medicine - perioperative care	1 (0.7)	—	1 (0.6)
	Internal medicine - Rheumatology	11 (7.7)	1 (5.9)	12 (7.5)
	Naturopathy	2 (1.4)	—	2 (1.3)
	Neurology	8 (5.6)	—	8 (5.0)
	OBGYN	1 (0.7)	—	1 (0.6)
	Orthopedic surgery	2 (1.4)	—	2 (1.3)
	Otolaryngology	1 (0.7)	—	1 (0.6)

	Physical medicine & Rehabilitation	4 (2.8)	1 (5.9)	5 (3.1)
	Pulmonary medicine	1 (0.7)	1 (5.9)	2 (1.3)
	Rheumatology	44 (30.8)	1 (5.9)	45 (28.1)
Specialty (Total)		88 (61.5)	4 (23.5)	92 (57.5)

APPENDIX N

Number of ICD-10 codes per referral for referrals included in analysis

No. of ICD-10 codes per referral	Referrals w referring provider's notes and/or indications (N=143)	Referrals w/o referring provider's notes or referring indications (N=17)	Total (N = 160)
Min-max	1-9	1-3	1-9
Mean	1.60	1.29	1.57
No.	N (%)	N (%)	N (%)
1	95 (66.4)	13 (76.5)	108 (67.5)
2	30 (21.0)	3 (17.6)	33 (20.6)
3	9 (6.3)	1 (5.9)	10 (6.3)
4	4 (2.8)	—	4 (2.5)
5	3 (2.1)	—	3 (1.9)
6	—	—	—
7	1 (0.7)	—	1 (0.6)
8	—	—	—
9	1 (0.7)	—	1 (0.6)

APPENDIX O

Number of CPT codes per referral for referrals included in analysis

No. of CPT codes per referral	Referrals w referring provider's notes and/or indications (N=143)	Referrals w/o referring provider's notes or referring indications (N=17)	Total (N = 160)
Min-max	1-6	1-4	1-6
Mean	1.65	1.59	1.64
No.	N (%)	N (%)	N (%)
1	77 (53.8)	11 (64.7)	88 (55.0)
2	47 (32.9)	3 (17.6)	50 (31.3)
3	15 (10.5)	2 (11.8)	17 (10.6)
4	2 (1.4)	1 (5.9)	3 (1.9)
5	—	—	—
6	2 (1.4)	—	2 (1.3)

APPENDIX P

Number of referrals per feature

Features	Referral provider checked and noted that the feature is present (i.e., positive) (N=143)	Referral provider checked and noted that the feature is absent (i.e., negative) (N=143)	Referral provider did not check (N=143)
	N (%)	N (%)	N (%)
Musculoskeletal findings			
arm span:height ratio >1.05	—	1 (0.7)	142 (99.3)
arthralgia/joint pain	72 (50.3)	5 (3.5)	66 (46.2)
chronic pain syndrome / chronic pain	5 (3.5)	—	138 (96.5)
dental crowding/high or narrow palate	2 (1.4)	—	141 (98.6)
dislocations	30 (21.0)	6 (4.2)	107 (74.8)
fatigue	41 (28.7)	7 (4.9)	95 (66.4)
fibromyalgia	21 (14.7)	—	122 (85.3)
joint hypermobility	84 (58.7)	6 (4.2)	53 (37.1)
joint stiffness	17 (11.9)	6 (4.2)	120 (83.9)
joint swelling	8 (5.6)	15 (10.5)	120 (83.9)
ligament / tendon tears	7 (4.9)	—	136 (95.1)
marfanoid / thin /tall habitus	5 (3.5)	—	138 (96.5)
multiple fractures	3 (2.1)	2 (1.4)	138 (96.5)
musculoskeletal pain	6 (4.2)	—	137 (95.8)
myalgia/muscle pain	10 (7.0)	2 (1.4)	131 (91.6)
myofascial pain / tenderness	8 (5.6)	—	135 (94.4)
osteoarthritis	1 (0.7)	—	142 (99.3)
pectus excavatum	4 (2.8)	—	139 (97.2)

pes planus/flat feet	3 (2.1)	—	140 (97.9)
scoliosis/kyphosis	12 (8.4)	1 (0.7)	130 (90.9)
sprains	7 (4.9)	—	136 (95.1)
subluxations/joint popping	13 (9.1)	—	130 (90.9)
temporomandibular joint dysfunction	9 (6.3)	—	134 (93.7)
thumb-wrist sign	—	1 (0.7)	142 (99.3)
Skin findings			
atrophic scarring	1 (0.7)	—	142 (99.3)
easy bruising	25 (17.5)	8 (5.6)	110 (76.9)
poor wound healing	5 (3.5)	3 (2.1)	135 (94.4)
skin elasticity/stretchy skin/hyperextensible skin/skin laxity	13 (9.1)	8 (5.6)	122 (85.3)
skin lesions/wounds	1 (0.7)	22 (15.4)	120 (83.9)
skin striae	1 (0.7)	—	142 (99.3)
thin skin/skin translucency	2 (1.4)	—	141 (98.6)
tissue fragility during surgery	1 (0.7)	—	142 (99.3)
velvety/"doughy" skin	1 (0.7)	—	142 (99.3)
Vascular findings			
aortic aneurysm	2 (1.4)	—	141 (98.6)
Vascular issues	1 (0.7)	1 (0.7)	141 (98.6)
Cardiac findings			
dilated aortic root	—	1 (0.7)	142 (99.3)
mitral valve prolapse	3 (2.1)	—	140 (97.9)
POTS	20 (14.0)	1 (0.7)	122 (85.3)
tachycardia	7 (4.9)	1 (0.7)	135 (94.4)
Gastrointestinal findings			
abdominal pain	24 (16.8)	20 (14.0)	99 (69.2)
GI disturbances	48 (33.6)	5 (3.5)	90 (62.9)

(constipation/diarrhea/irritable bowel syndrome/disease)			
Genitourinary / Gynecological findings			
hernia	1 (0.7)	2 (1.4)	140 (97.9)
history of organ prolapse (exclude mitral valve)	2 (1.4)	1 (0.7)	140 (97.9)
history of organ rupture	—	3 (2.1)	140 (97.9)
Respiratory findings			
pneumothorax	2 (1.4)	—	141 (98.6)
Eye findings			
eye findings	7 (4.9)	4 (2.8)	132 (92.3)
Hematologic / Immunologic findings			
Excessive / easy bleeding / bleeding issue	5 (3.5)	4 (2.8)	134 (93.7)
mast cell / MCAS / mastocytosis	5 (3.5)	—	138 (96.5)
Neurological findings			
brain fog	4 (2.8)	1 (0.7)	138 (96.5)
dizziness	23 (16.1)	8 (5.6)	112 (78.3)
dysautonomia	3 (2.1)	—	140 (97.9)
headaches / migraines	35 (24.5)	11 (7.7)	97 (67.8)
lightheaded	10 (7.0)	4 (2.8)	129 (90.2)
memory problems	1 (0.7)	2 (1.4)	140 (97.9)
poor balance / balance problem	—	2 (1.4)	141 (98.6)
presyncope / syncope	12 (8.4)	9 (6.3)	122 (85.3)
Behavioral/Developmental Findings			
anxiety / depression	46 (32.2)	7 (4.9)	90 (62.9)
insomnia / poor sleep	16 (11.2)	7 (4.9)	120 (83.9)

APPENDIX Q

Primary indication for referral to genetics

Along with the statement "Refer to genetics for…" or written in referral indications

Indications	Primary indication for referral to genetics (N=143)	
	Details (if applicable)	N (%)
Evaluation for/rule out CTD		18 (11.2)
Evaluation for/rule out EDS		86 (60.1)
Patient referral desire		19 (13.3)
Patient suspects EDS/CTD		5 (3.5)
Pt "been told they have EDS"/there has been concern for EDS		2 (1.4)
Joint hypermobility (JH)		60 (42.0)
CTD-suspected history (except JH) (e.g., dislocations, easy bruising)		34 (23.8)
Features commonly associated with CTD (e.g., pain, POTS)		32 (22.4)
Previous diagnosis	EDS	2 (1.4)
	Hypermobile EDS	3 (2.1)
	Vascular EDS (vEDS)	1 (0.7)
	"Vascular issues related to EDS"	1 (0.7)
	"Childhood EDS"	1 (0.7)
	(Total)	8 (5.6)
Genetic testing	Previously tested (VUS on EDS panel)	1 (0.7)
	Previously tested (vEDS)	1 (0.7)
	For CTD	1 (0.7)

	"Collagen testing"	1 (0.7)
	For EDS	18 (12.6)
	For classical EDS	1 (0.7)
	For vascular EDS	1 (0.7)
	For Marfan syndrome	3 (2.1)
	For EDS and Marfan syndrome	1 (0.7)
	Unspecified	6 (4.2)
	(Total)	34 (23.8)
Family history	EDS	6 (4.2)
	Hypermobile EDS	1 (0.7)
	vEDS and aortic rupture	1 (0.7)
	"Showing signs of possible EDS"	1 (0.7)
	Joint hypermobility (JH)	5 (3.5)
	JH, Marfan syndrome, and mitral valve prolapse	1 (0.7)
	Mitral valve disorders, ventral septal defect, marfanoid habitus	1 (0.7)
	JH and aneurysm	1 (0.7)
	Aneurysm	1 (0.7)
	Aortic aneurysm	2 (1.4)
	Aortic dissection	1 (0.7)
	Pectus excavatum	1 (0.7)
	Pneumothorax	1 (0.7)
	(Total)	23 (16.1)

APPENDIX R

Possible referral indications mentioned in referring provider's clinical documentation

Possible indications	Mentioned in referring provider's clinical documentation (N=143)	
	Details (if applicable)	N (%)
Evaluation for/rule out CTD		5 (3.5)
Evaluation for/rule out EDS		8 (5.6)
Patient referral desire		8 (5.6)
Patient suspects EDS/CTD		16 (11.2)
Pt "been told they have EDS"/there has been concern for EDS		13 (9.1)
Joint hypermobility (JH)		27 (18.9)
CTD-suspected history (except JH) (e.g., dislocations, easy bruising)		35 (24.5)
Features commonly associated with CTD (e.g., pain, POTS)		33 (23.1)
Previous diagnosis	JHS/HSD	1 (0.7)
	Hypermobile EDS (hEDS)	2 (1.4)
	EDS	6 (4.2)
	(Total)	9 (6.3)
Genetic testing	For CTD	1 (0.7)
	For EDS	7 (4.9)
	Previous testing for EDS	1 (0.7)
	"Previous testing" for hEDS	1 (0.7)
	Previous testing with result	1 (0.7)

	(Total)	11	(5.6)
Family history	EDS	3	(2.1)
	"Markers" for "MD" [a] and EDS	1	(0.7)
	CTD in "collagen type II"	1	(0.7)
	Joint hypermobility (JH)	2	(1.4)
	JH and Dislocation	1	(0.7)
	JH and ophthalmological finding	1	(0.7)
	Aortic aneurysm	1	(0.7)
	Tall	1	(0.7)
	POTS and sprains	1	(0.7)
	(Total)	12	(8.4)

[a] Possibly muscular dystrophy - unspecified in the clinical documentation.

APPENDIX S

Referral classification distribution by factors associated with referrals

	Appropriate	Context -dependent	Missing details	Inappropriate	Total (N=143)
Sex assigned at birth					
Female	51 (40.8)	23 (18.4)	40 (32.0)	11 (8.8)	125 (87.4)
Male	7 (38.9)	6 (33.3)	5 (27.8)	—	18 (12.6)
Referral class					
Internal	27 (46.7)	14 (24.1)	12 (20.7)	5 (8.6)	58 (40.6)
External	31 (36.5)	15 (17.6)	33 (38.8)	6 (7.1)	85 (59.4)
Referring provider specialty[a]					
Primary care	18 (32.7)	8 (14.5)	26 (47.3)	3 (5.5)	55 (38.5)
Specialists	40 (45.5)	21 (23.9)	19 (21.6)	8 (9.1)	88 (61.5)
Referral priority					
Routine	48 (37.8)	26 (20.5)	42 (33.1)	11 (8.7)	127 (88.8)
Others[b]	10 (62.5)	3 (18.8)	3 (18.8)	—	16 (11.2)
Insurance types (federal vs. commercial)[c]					
Federal	22 (40.0)	15 (27.3)	17 (30.9)	1 (1.8)	55 (38.5)
Commercial	36 (40.9)	14 (15.9)	28 (31.8)	10 (11.4)	88 (61.5)
Insurance types (auth required vs. no auth required)[d]					
Auth required	29 (39.2)	18 (24.3)	22 (29.7)	5 (6.8)	74 (51.7)
No auth required	29 (42.0)	11 (15.9)	23 (33.3)	6 (8.7)	69 (48.3)

[a] See Appendix M to see the groupings of the referring provider specialties.

[b] Other referral priorities aside from routine include: stat, urgent, and emergency.

[c] See Table 8 to see the groupings of the insurances.

APPENDIX T

Full list of ICD-10 codes associated with referrals with or without provider's clinical documentation and the grouping by relevance to hEDS/CTD

ICD-10 codes	Code titles	Grouping
D50.8	Other iron deficiency anemias	Unrelated to hEDS
D70.9	Neutropenia, unspecified	Unrelated to hEDS
D80.8	Other immunodeficiencies with predominantly antibody defects	Unrelated to hEDS
D89.40	Mast cell activation, unspecified	Commonly associated with hEDS
D89.9	Disorder involving the immune mechanism, unspecified	Unrelated to hEDS
E88.2	Lipomatosis, not elsewhere classified	Unrelated to hEDS
G24.1	Genetic torsion dystonia	Commonly associated with hEDS
G61.81	Chronic inflammatory demyelinating polyneuritis	Unrelated to hEDS
G62.81	Critical illness polyneuropathy	Unrelated to hEDS
G89.29	Other chronic pain	May be a part of hEDS
G90.1	Familial dysautonomia	Commonly associated with hEDS
G90.2	Horner's syndrome	Unrelated to hEDS
G90.A	Postural orthostatic tachycardia syndrome [POTS]	Commonly associated with hEDS
H20.9	Unspecified iridocyclitis	Unrelated to hEDS
I47.1	Supraventricular tachycardia	Commonly associated with hEDS
I49.8	Other specified cardiac arrhythmias	Commonly associated with hEDS
I72.0	Aneurysm of carotid artery	CTD feature

I73.00	Raynaud's syndrome without gangrene	Unrelated to hEDS
I77.71	Dissection of carotid artery	CTD feature
I95.9	Hypotension, unspecified	Commonly associated with hEDS
J34.3	Hypertrophy of nasal turbinates	Unrelated to hEDS
J34.89	Other specified disorders of nose and nasal sinuses	Unrelated to hEDS
J45.21	Mild intermittent asthma with (acute) exacerbation	Unrelated to hEDS
J93.9	Pneumothorax, unspecified	CTD feature
K58.9	Irritable bowel syndrome without diarrhea	Commonly associated with hEDS
L65.9	Nonscarring hair loss, unspecified	Unrelated to hEDS
L70.9	Acne, unspecified	Unrelated to hEDS
M13.0	Polyarthritis, unspecified	May be a part of hEDS
M24.276	Disorder of ligament, unspecified foot	May be a part of hEDS
M24.419	Recurrent dislocation, unspecified shoulder	May be a part of hEDS
M24.80	Other specific joint derangements of unspecified joint, not elsewhere classified	May be a part of hEDS
M24.9	Joint derangement, unspecified	May be a part of hEDS
M25.50	Pain in unspecified joint	May be a part of hEDS
M25.511	Pain in right shoulder	May be a part of hEDS
M35.7	Hypermobility syndrome	CTD feature
M35.9	Systemic involvement of connective tissue, unspecified	CTD feature
M50.20	Other cervical disc displacement, unspecified cervical region	May be a part of hEDS
M54.9	Dorsalgia, unspecified (back pain)	May be a part of hEDS
M79.10	Myalgia, unspecified site	May be a part of hEDS
M79.18	Myalgia, other site	May be a part of hEDS

M79.7	Fibromyalgia	May be a part of hEDS
Q67.6	Pectus excavatum	CTD feature
Q79.6	Ehlers-Danlos syndromes	CTD
Q79.60	Ehlers-Danlos syndrome, unspecified	CTD
Q79.62	Hypermobile Ehlers-Danlos syndrome	CTD
Q79.69	Other Ehlers-Danlos syndromes	CTD
Q87.40	Marfan's syndrome, unspecified	CTD
R00.0	Tachycardia, unspecified	Commonly associated with hEDS
R00.1	Bradycardia, unspecified	Unrelated to hEDS
R01.1	Cardiac murmur, unspecified	CTD feature
R10.31	Right lower quadrant pain	Nonspecific
R23.3	Spontaneous ecchymoses	CTD feature
R23.8	Other skin changes	Nonspecific
R29.898	Other symptoms and signs involving the musculoskeletal system	CTD feature
R42	Dizziness and giddiness	Commonly associated with hEDS
R51.9	Headache, unspecified	Commonly associated with hEDS
R53.83	Other fatigue	Commonly associated with hEDS
R55	Syncope and collapse	Commonly associated with hEDS
R68.89	Other general symptoms and signs	Nonspecific
R69	Illness, unspecified	Nonspecific
R76.8	Other specified abnormal immunological findings in serum	Unrelated to hEDS
R79.89	Other specified abnormal findings of blood chemistry	Unrelated to hEDS

T07.XXXA	Unspecified multiple injuries, initial encounter	Nonspecific
Z80.3	Family history of malignant neoplasm of breast	Unrelated to hEDS
Z82.49	Family history of ischemic heart disease and other diseases of the circulatory system	CTD feature
Z82.69	Family history of other diseases of the musculoskeletal system and connective tissue	CTD feature
Z86.61	Personal history of infections of the central nervous system	Unrelated to hEDS
Z86.69	Personal history of other diseases of the nervous system and sense organs	Unrelated to hEDS
Z87.898	Personal history of other specified conditions	Nonspecific
Z98.890	Other specified postprocedural states	Nonspecific
Z99.3	Dependence on wheelchair	Nonspecific

Descriptions from: ICD9Data.com, ICD10Data.com (accessed May 20th, 2023).

APPENDIX U

Number of referrals per ICD-10 code

ICD-10 codes	Referrals w referring provider's notes and/or indications (N=229)	Referrals w/o referring provider's notes or referring indications (N=22)	Total (N=251)
	N (%)	N (%)	N (%)
D50.8	1 (0.4)	—	1 (0.4)
D70.9	1 (0.4)	—	1 (0.4)
D80.8	1 (0.4)	—	1 (0.4)
D89.40	2 (0.9)	—	2 (0.8)
D89.9	1 (0.4)	—	1 (0.4)
E88.2	1 (0.4)	—	1 (0.4)
G24.1	1 (0.4)	—	1 (0.4)
G61.81	1 (0.4)	—	1 (0.4)
G62.81	1 (0.4)	—	1 (0.4)
G89.29	1 (0.4)	—	1 (0.4)
G90.1	2 (0.9)	1 (4.5)	3 (1.2)
G90.2	1 (0.4)	—	1 (0.4)
G90.A	3 (1.3)	—	3 (1.2)
H20.9	1 (0.4)	—	1 (0.4)
I47.1	1 (0.4)	—	1 (0.4)
I49.8	6 (2.6)	—	6 (2.4)
I72.0	1 (0.4)	—	1 (0.4)
I73.00	1 (0.4)	—	1 (0.4)
I77.71	1 (0.4)	—	1 (0.4)

I95.9	1 (0.4)	—	1 (0.4)
J34.3	1 (0.4)	—	1 (0.4)
J34.89	1 (0.4)	—	1 (0.4)
J45.21	1 (0.4)	—	1 (0.4)
J93.9	1 (0.4)	—	1 (0.4)
K58.9	1 (0.4)	—	1 (0.4)
L65.9	1 (0.4)	—	1 (0.4)
L70.9	1 (0.4)	—	1 (0.4)
M13.0	1 (0.4)	—	1 (0.4)
M24.276	1 (0.4)	—	1 (0.4)
M24.419	1 (0.4)	—	1 (0.4)
M24.80	2 (0.9)	—	2 (0.8)
M24.9	23 (10.0)	1 (4.5)	24 (9.6)
M25.50	24 (10.5)	—	24 (9.6)
M25.511	1 (0.4)	—	1 (0.4)
M35.7	31 (13.5)	6 (27.3)	37 (14.7)
M35.9	2 (0.9)	2 (9.1)	4 (1.6)
M50.20	1 (0.4)	—	1 (0.4)
M54.9	1 (0.4)	—	1 (0.4)
M79.10	1 (0.4)	—	1 (0.4)
M79.18	1 (0.4)	—	1 (0.4)
M79.7	2 (0.9)	1 (4.5)	3 (1.2)
Q67.6	3 (1.3)	—	3 (1.2)
Q79.6	2 (0.9)	1 (4.5)	3 (1.2)
Q79.60	54 (23.6)	5 (22.7)	59 (23.5)
Q79.62	4 (1.7)	1 (4.5)	5 (2.0)

Q79.69	1 (0.4)	—	1 (0.4)
Q87.40	3 (1.3)	—	3 (1.2)
R00.0	1 (0.4)	—	1 (0.4)
R00.1	1 (0.4)	—	1 (0.4)
R01.1	1 (0.4)	—	1 (0.4)
R10.31	1 (0.4)	—	1 (0.4)
R23.3	1 (0.4)	1 (4.5)	2 (0.8)
R23.8	1 (0.4)	1 (4.5)	2 (0.8)
R29.898	1 (0.4)	—	1 (0.4)
R42	3 (1.3)	—	3 (1.2)
R51.9	1 (0.4)	—	1 (0.4)
R53.83	3 (1.3)	—	3 (1.2)
R55	2 (0.9)	1 (4.5)	3 (1.2)
R68.89	1 (0.4)	—	1 (0.4)
R69	1 (0.4)	—	1 (0.4)
R76.8	1 (0.4)	—	1 (0.4)
R79.89	1 (0.4)	—	1 (0.4)
T07.XXXA	1 (0.4)	—	1 (0.4)
Z80.3	1 (0.4)	—	1 (0.4)
Z82.49	4 (1.7)	—	4 (1.6)
Z82.69	3 (1.3)	1 (4.5)	4 (1.6)
Z86.61	1 (0.4)	—	1 (0.4)
Z86.69	1 (0.4)	—	1 (0.4)
Z87.898	1 (0.4)	—	1 (0.4)
Z98.890	1 (0.4)	—	1 (0.4)
Z99.3	1 (0.4)	—	1 (0.4)

APPENDIX V

Full list of ICD-10 codes with distribution of appropriateness classification of the 143 referrals

ICD-10 codes	Appropriate	Context-dependent	Missing details	Inappropriate
N=229	N (%)	N (%)	N (%)	N (%)
D50.8	—	—	—	1 (100.0)
D70.9	1 (100.0)	—	—	—
D80.8	—	1 (100.0)	—	—
D89.40	—	—	2 (100.0)	—
D89.9	—	—	1 (100.0)	—
E88.2	—	—	1 (100.0)	—
G24.1	—	1 (100.0)	—	—
G61.81	—	—	1 (100.0)	—
G62.81	—	—	1 (100.0)	—
G89.29	—	—	1 (100.0)	—
G90.1	—	1 (50.0)	—	1 (50.0)
G90.2	1 (100.0)	—	—	—
G90.A	1 (33.3)	1 (33.3)	1 (33.3)	—
H20.9	1 (100.0)	—	—	—
I47.1	—	—	1 (100.0)	—
I49.8	1 (16.7)	2 (33.3)	2 (33.3)	1 (16.7)
I72.0	1 (100.0)	—	—	—
I73.00	1 (100.0)	—	—	—
I77.71	1 (100.0)	—	—	—
I95.9	1 (100.0)	—	—	—

J34.3	—	—	—	1 (100.0)
J34.89	—	—	—	1 (100.0)
J45.21	—	—	—	1 (100.0)
J93.9	1 (100.0)	—	—	—
K58.9	—	—	—	1 (100.0)
L65.9	1 (100.0)	—	—	—
L70.9	1 (100.0)	—	—	—
M13.0	1 (100.0)	—	—	—
M24.276	—	—	1 (100.0)	—
M24.419	1 (100.0)	—	—	—
M24.80	1 (50.0)	—	1 (50.0)	—
M24.9	8 (34.8)	5 (21.7)	9 (39.1)	1 (4.3)
M25.50	9 (37.5)	4 (16.7)	8 (33.3)	3 (12.5)
M25.511	—	1 (100.0)	—	—
M35.7	18 (58.1)	4 (12.9)	9 (29.0)	—
M35.9	1 (50.0)	1 (50.0)	—	—
M50.20	—	—	1 (100.0)	—
M54.9	—	—	1 (100.0)	—
M79.10	1 (100.0)	—	—	—
M79.18	—	1 (100.0)	—	—
M79.7	—	1 (50.0)	1 (50.0)	—
Q67.6	2 (66.7)	1 (33.3)	—	—
Q79.6	1 (50.0)	—	1 (50.0)	—
Q79.60	22 (40.7)	10 (18.5)	16 (29.6)	6 (11.1)
Q79.62	—	3 (75.0)	1 (25.0)	—
Q79.69	1 (100.0)	—	—	—

Q87.40	1 (33.3)	2 (66.7)	—	—
R00.0	1 (100.0)	—	—	—
R00.1	1 (100.0)	—	—	—
R01.1	—	—	1 (100.0)	—
R10.31	—	1 (100.0)	—	—
R23.3	—	1 (100.0)	—	—
R23.8	—	1 (100.0)	—	—
R29.898	1 (100.0)	—	—	—
R42	2 (66.7)	1 (33.3)	—	—
R51.9	—	—	1 (100.0)	—
R53.83	2 (66.7)	—	1 (33.3)	—
R55	2 (100.0)	—	—	—
R68.89	1 (100.0)	—	—	—
R69	1 (100.0)	—	—	—
R76.8	1 (100.0)	—	—	—
R79.89	—	—	1 (100.0)	—
T07.XXXA	1 (100.0)	—	—	—
Z80.3	—	—	1 (100.0)	—
Z82.49	4 (100.0)	—	—	—
Z82.69	1 (33.3)	2 (66.7)	—	—
Z86.61	1 (100.0)	—	—	—
Z86.69	—	—	1 (100.0)	—
Z87.898	1 (100.0)	—	—	—
Z98.890	—	—	—	1 (100.0)
Z99.3	1 (100.0)	—	—	—

APPENDIX W

Number of referrals per CPT code

CPT codes	Referrals w referring provider's notes and/or indications (N=236)	Referrals w/o referring provider's notes or referring indications (N=27)	Total (N=263)
	N (%)	N (%)	N (%)
96040	18 (7.6)	3 (11.1)	21 (8.0)
99203	6 (2.5)	2 (7.4)	8 (3.0)
99204	21 (8.9)	6 (22.2)	27 (10.3)
99205	50 (21.2)	6 (22.2)	56 (21.3)
99213	2 (0.8)	—	2 (0.8)
99214	3 (1.3)	—	3 (1.1)
99215	8 (3.4)	2 (7.4)	10 (3.8)
99243	1 (0.4)	—	1 (0.4)
99244	1 (0.4)	—	1 (0.4)
99245	19 (8.1)	4 (14.8)	23 (8.7)
99354	2 (0.8)	—	2 (0.8)
99355	2 (0.8)	—	2 (0.8)
99358	2 (0.8)	—	2 (0.8)
99359	2 (0.8)	—	2 (0.8)
99417	1 (0.4)	—	1 (0.4)
CON9509	71 (30.1)	3 (11.1)	74 (28.1)
N99204	2 (0.8)	—	2 (0.8)
S0265	18 (7.6)	—	18 (6.8)
Z7500	7 (3.0)	1 (3.7)	8 (3.0)