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Exploring Evidence for Utility of Genomic Medicine Approaches for Individuals, Families and Society

THESIS

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MASTER OF SCIENCE

in Genetic Counseling

by

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2021
DEDICATION

For

Laurie

my earliest partner in solving medical mysteries
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ABSTRACT OF THE THESIS

Exploring Evidence for Utility of Genomic Medicine Approaches for Individuals, Families and Society

by

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Genomic medicine holds promise to significantly improve human health. While a growing body of evidence suggests genomic approaches can improve disease management, more evidence – particularly on adults and individuals of non-European ancestry and lower socioeconomic status – is needed on clinical utility to spur widespread clinical implementation. Through a retrospective chart review of referrals and genetics consultation notes at one adult genetics clinic, this study explored evidence for utility of genomic medicine approaches for individuals, families and society.

The study demonstrated a genomic testing diagnostic yield of 36%. Individuals who did not report European ancestry were more likely to be diagnosed via genomic testing (69%) than those of European ancestry (26%). The mean number of specialists previously seen was 2.9. The mean years from first symptom to genetics evaluation was 15.6 years. Significantly more in-person patients followed through on testing than did telemedicine patients (77% versus 42%). Telemedicine patients experienced a quicker turnaround time from appointment to results than in-person patients. Twenty-five percent of patients
received a referral to at least one medical specialist. Ninety percent of patients suspected to have a genetic condition received condition education. Seven percent of patients were prescribed a treatment. Sixteen percent of those suspected to have a genetic condition received resources.

Inheritance pattern education was provided for 83%. Cascade testing for family members was recommended 54% of the time in diagnosed patients. Twenty-three percent of diagnosed patients received a family letter.

Clinical notes documenting visits were sent to primary care physicians or referring providers in nearly every instance (98%). Two percent of patients suspected to have a genetic condition were referred for research participation after the clinic visit.

The study demonstrated a genomic testing diagnostic yield in line with the literature and confirmed and further delineated the “diagnostic odyssey” experienced by rare disease patients, as well as the test ordering and completion processes in an adult population. It documented individuals, family and society are receiving services beyond diagnosis and medical management, such as education, resources and referrals – offerings likely construed as valuable. In so doing this study offers insights into opportunities and challenges for the health care community to consider when implementing genomic medicine approaches and caring for patients.
INTRODUCTION

“Progress in genomics since the completion of the Human Genome Project has exceeded even optimistic expectations in terms of discoveries about the genetic basis of health and disease. Knowledge about the clinical relevance of genomic variants is growing in leaps and bounds – and the new and exciting challenge is to turn that knowledge into more effective healthcare.”
– National Human Genome Research Institute (NHGRI) Director Eric Green, M.D., Ph.D., upon the establishment of NHGRI’s new intramural precision health research program, February 12, 2020

I. The burden of rare disease

More than 7,000 rare diseases (80% with a genetic component) affect approximately 400 million people worldwide (Global Genes, 2021). Genetic disorders represent an important cause of stillbirths, child mortality and ongoing disability (Blencowe et al., 2018). While overall child mortality rates have largely decreased in recent decades due to reductions in deaths from infections, diarrhea and vaccine-preventable diseases, non-communicable conditions, such as genetic disorders, now make up a larger relative proportion of all deaths under the age of five (Liu et al., 2016). Three to 10% of all hospitalizations (regardless of age) are related to a rare disease (Global Genes, 2021). Adults with rare diseases report lower health-related quality of life compared with the general population and patients with common chronic diseases (Bogart & Irvin, 2017).

As Blencowe et al. (2018) explain, genetic disorders can be divided into two broad groups: “single-gene,” meaning they are caused by variants in a single gene with strong effect and “genetic risk factors,” meaning gene variants with weaker effect cause disease only when combined with other genetic and/or environmental factors. Single-gene disorders generally follow Mendelian inheritance patterns, which include autosomal dominant, autosomal
recessive and X-linked. Single-gene disorders can be divided further into “common” and “rare.” Many common single-gene disorders are characterized by a causative gene variant shown to confer a selective advantage in a local environment, such as sickle cell anemia. In other common single-gene disorders, such as hereditary hemochromatosis, hypotheses exist for such advantages. “Rare” single-gene disorders such as osteogenesis imperfecta affect a small number of individuals. However, when rare single gene disorders are considered collectively, they account for a significant public health burden. Knowing the specific genetic cause responsible for a given rare disease can help inform clinical management, guide therapeutic strategies, and provide value information and counseling to families (Blencowe et al., 2018).

Historically, except in the case of a few conditions with pathognomonic presentations, finding these specific genetic causes has often been a complicated process, and targeted treatment largely lacking. Many, especially those with rare disorders, face a “diagnostic odyssey,” a years-long process involving multiple specialists, lengthy documentation of clinical manifestations, imaging and biochemical tests, which often has a low success rate (Fernandez-Marmiesse et al., 2018). It has been estimated that getting an accurate rare disease diagnosis can take six-to-eight years and require an average of 7.3 physician consults (Global Genes, 2021; Global Genes, 2013). Further, while significant progress is being made in regard to treatment, 95% of all rare diseases do not have a treatment approved by the U.S. Food and Drug Administration and fewer than one in 10 patients with a rare disease receives disease-specific treatment (Global Genes, 2021).
II. The Human Genome Project and the promise of precision medicine

Gene sequencing, a technology used to assess variation in the genetic code, has long been widely accepted in clinical diagnostics of genetic disease. In the mid-1970’s, more than two decades after James Watson and Francis Crick described the double helix structure of DNA in 1953, the nearly simultaneous development of Maxam-Gilbert and Sanger sequencing made sequencing available from a research perspective. The Sanger method, also known as the chain-termination or dideoxy method, involves synthesizing DNA chains of varying lengths through the inclusion of dideoxynucleotide triphosphates (ddNTPs) which inhibit further strand extension (Dewey et al., 2012). The strands of varying lengths are then separated by size using gel or capillary tube electrophoresis, enabling researchers to distinguish DNA fragments that differ in size by only a single nucleotide (Adams, 2008). A typical Sanger sequencing experiment results in 500–600 base pairs of sequence and covers, on average, a single exon of a gene (Shevchenko & Bale, 2016).

As Dewey et al. (2012) explain, Sanger sequencing became the research and commercial standard due to technical ease and reliability of results, and remained so for over three decades. It was the method used to define the basis of many Mendelian disorders. Today, Sanger sequencing remains the method of choice for sequencing short segments of DNA and confirming genotypes from other technologies (Dewey et al., 2012).

Importantly, a modified Sanger approach formed the basis of the first draft human genome sequence. Researchers working simultaneously as part of two efforts – the publicly funded Human Genome Project (HGP) and Craig Venter and colleagues at the Celera Corporation – produced this genome sequence through a method called “shotgun
sequencing” (sequencing 500 to 600 base pair segments of DNA in parallel) and then “assembling” these sequence fragments into contiguous stretches of DNA based on sequence overlap (Dewey et al., 2012).

The HGP has been called “the single most important project in biology and the biomedical services” (Collins et al., 1998). An international effort formally begun in October 1990, HGP was sponsored in the United States by the Department of Energy Human Genome Program and the National Institutes of Health’s NHGRI. Its primary goals were to: discover all of the estimated 20,000 genes in the human genome so they could be used for future scientific study; and to sequence completely the genome’s 3 billion DNA base-pairs (Human Genome Project Information Archive 1990-2003, 2021). By its completion in 2003, HGP had met these goals, producing an “essentially finished” version of the human genome sequence, and also achieving other milestones, such as creating physical and genetic maps of the human genome and mapping and sequencing five model organisms, including the mouse (NIH NHGRI Human Genome Project FAQ, 2020).

These achievements, along with concurrent advancements in “big data” analysis, also paved the way for a variety of cost-effective, high-throughput sequencing (HTS; also known as “next-generation sequencing, or NGS”) technologies, advancing the field of genomics significantly. Whereas generating the first complete human genome sequence through the HGP utilizing traditional Sanger sequencing took 13 years, at an estimated cost of $500 million to $1 billion, today’s NGS technologies utilized by sequencing centers and laboratories can accomplish the same in as little as one day and for as little as $1,000 (NIH NHGRI The cost of sequencing a human genome, 2020; Reuter et al., 2015). Additionally, NGS
now has applications beyond sequencing human genomes; it has enabled the characterization and study of other “omics,” including surrounding the transcriptome, proteome, metabolome, epigenome and others, in a variety of organisms (Ghosh and Poisson, 2009; Moreno-Risueno et al., 2010; Reuter et al., 2015).

From its earliest days, the HGP generated widespread excitement about its potential to usher in a new era of “precision medicine,” in which individualized genetic information could be used to more accurately assess disease risk, guide diagnosis and provide the right drug, in the right dose, to the right patient at the right time (NIH NHGRI Genomics and medicine, 2020). The promise of precision medicine – which would replace the traditional “one-size-fits-all” approach – lies in the ability for health care providers to take proactive rather than reactive actions. The theory goes that it could lead to earlier diagnosis, fewer medication side effects and less toxicity and improved health outcomes, thus reducing financial and time expenditures and improving patients’ quality of life (Mathur & Sutton, 2017).

Underpinning the success of precision medicine is genomic medicine. According to NHGRI, genomic medicine is defined as “an emerging medical discipline that involves using genomic information about an individual as part of their clinical care (e.g., for diagnostic or therapeutic decision-making) and the health outcomes and policy implications of that clinical use” (NIH NHGRI Genomics and medicine, 2020). It is widely accepted that NGS has transformed genomic medicine. NGS technology is the backbone of the tools now regularly used in the genetics clinic, including gene panels (∼10–200 genes), exomes (∼20,000 genes) and whole human genomes (6 gigabase pairs), diagnostics in solid tumors and infectious
diseases, as well as noninvasive prenatal testing (Shevchenko & Bale, 2016). These tools have improved understanding of the connection between certain sequence variants and disease and identified new disorders. Increased adoption of sequencing as a cost-effective, rapid, clinical genomic medicine tool has also enabled comprehensive detection of genetic variation (Goodwin et al., 2016; Neu et al., 2019; NIH NHGRI The cost of sequencing a human genome, 2020).

Whereas Sanger sequencing could previously serve as an accurate diagnostic tool when there were clear signs of a single-gene disorder, NGS has proven useful in clinically heterogenous disorders, such as cancer, cardiomyopathies, connective tissue disorders and autism (Di Resta et al., 2018). Additionally, with NGS, clinicians are able to better account for the influence of mosaic and de novo mutations and a spectrum of phenotypes, and detect the presence of more than one variant in a single patient. Superior, more targeted therapies have also been introduced, earlier in the disease course, and this is an active area of research (Fernandez-Marmiesse et al., 2018).

Oncology is often used as an example of a specialty in which precision medicine approaches are altering the clinical paradigm. For example, discovery of the \textit{BRCA1} and \textit{BRCA2} genes in families with strong histories of breast and ovarian cancer in 1990 opened the door for the identification of other rare yet highly penetrant genes that confer distinct clinical cancer syndromes when mutated, such as \textit{PTEN}, \textit{TP53}, \textit{CHD1} and \textit{STK11}. The ability to recognize individuals with one of these hereditary cancer syndromes greatly affects clinical management of individuals, as well as of their potentially affected family members (Shiovitz & Korde, 2015), including through providing prophylactic surgery options,
increased surveillance recommendations, guiding treatment strategies and conferring family planning considerations. Additionally, the first cancer genome draft quickly followed the human genome draft. That information has since formed the basis of targeted prognostic and diagnostic tools of which clinicians now regularly avail themselves, including liquid biopsies and tumor profiling, as well as molecular-guided therapies (Schwartzberg et al., 2017).

III. The role of the genetics specialty

The genetics clinic is the referral destination when a condition with an underlying genetic etiology is suspected. According to the American College of Medical Genetics and Genomics (ACMG Careers in Medical Genetics, 2021), medical genetics health care teams can include clinical geneticists, laboratory geneticists, genetic counselors, nurses, physician assistants, metabolic dietitians, and more.

Clinical geneticists are medical doctors responsible for caring for patients in the genetics clinic. They receive broad-based training in the evaluation, diagnosis, management and treatment of inherited conditions in children and adults and hold American Board of Medical Genetics and Genomics (ABMGG) certification in the specialty of clinical genetics and genomics. Clinical geneticists hold degrees such as MD, DO or the equivalent and complete at least one residence year in an Accreditation Council for Graduate Medical Education (ACGME)-accredited primary specialty followed by two years of medical genetics and genomics residency training (ACMG Careers in Medical Genetics, 2021).

As the American Medical Association (2021) notes, clinical geneticists diagnose genetic conditions, implement treatment plans and provide genetic counseling to patients and families in a variety of settings, including fertility/preconception, prenatal, pediatric,
adult and cancer. Genetic diseases under their purview may include single gene and chromosomal disorders, congenital anomalies, inborn errors of metabolism, multifactorial conditions, and common disorders with hereditary factors. Underpinning these roles are cytogenetic, molecular, genomic and biochemical testing. More and more, as the role of genetics in common disease, such as diabetes and heart disease, are becoming better understood, medical geneticists are involved in the care of these patients as well, and are being engaged by other health care professionals for their expertise.

Genetic counselors are health care professionals with advanced training in medical genetics and genomics and counseling. They work in clinical, laboratory, research, public health and other settings where genetic and genomic education, tests and services are delivered under the supervision of a medical geneticist or other physician. Genetic counselors hold bachelor’s degrees and complete two-year master’s degree programs accredited by the Accreditation Council for Genetic Counseling (ACGC). Candidates graduating from an accredited master’s degree program in genetic counseling are eligible to seek board certification through the American Board of Genetic Counseling, Inc. (ABGC). Additionally, an increasing number of states now require licensure to practice as a genetic counselor (ACMG Careers in Medical Genetics, 2021, National Society of Genetic Counselors [NSGC] States Issuing Licenses for Genetic Counselors, 2021).

In 2006, the Genetic Counseling Definition Task Force of the NSGC developed a revised definition of genetic counseling that was approved by the NSGC Board of Directors: “Genetic counseling is the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease. This process integrates the following: interpretation of family and medical histories to assess the chance
of disease occurrence or recurrence; education about inheritance, testing, management, prevention, resources and research; and counseling to promote informed choices and adaptation to the risk or condition” (NSGC’s Definition Task Force). More specifically, the components of the genetic counseling interaction have been described as including: information gathering; obtaining family history recorded in the form of a pedigree; documenting medical history and determining the individual’s or family’s understanding and beliefs about reason for referral; establishing or verifying diagnosis, which can include physical examination conducted by the clinical geneticist, diagnostic procedure, such as prenatal or other genetic testing; risk assessment, including on personal future reproductive and/or personal health risk; information giving, which can include explaining the condition, as well as its presentation, variability and natural history, description of the medical, surgical, social and educational interventions available to treat and condition and/or manage its symptoms, and discussion on relevant financial and psychosocial resources (e.g., support groups, web-based information); and psychological counseling and support, or preparing patients for the oftentimes powerful emotional responses that can accompany genetic diagnosis or information, as well as offering ways to cope (Uhlmann et al., 2009, p. 11-14). Of note, physical examination is not only important for an initial suspected clinical diagnosis; it also assists the laboratory in conducting appropriate analysis and interpretation, including variant interpretation (Rehm et al., 2013). Regardless of the testing strategy ultimately employed, it is recommended that ordering clinical geneticists provide detailed phenotypic information to the laboratory. Clinical geneticists and genetic counselors also frequently provide referrals to other specialists for follow-up examinations or imaging.
Perhaps the most fundamental component of the genetic counseling process is the ascertainment of an accurate, detailed family history that compiles information about the physical and mental health of an individual’s family. The family history serves as the basis for making a diagnosis, determining risk, making medical management recommendations and assessing needs for patient education and psychosocial support (Uhlmann et al., 2009, p. 37). Clinician interpretations of the significance of family history ultimately need to take into account issues of variable expressivity (that is, the degree to which a phenotype is expressed by an individual with a particular genotype) and degree of penetrance (that is, the likelihood that a particular phenotype will occur when a particular genotype is present) of specific gene mutations. Reduced penetrance is not uncommon in genetic disease, and the penetrance of certain conditions is known to be age- or sex-dependent.

As Bennett writes, the process of taking a pedigree has another function during the patient visit, as well: establishing rapport and facilitating decision-making. Patients are known to be more likely to comply with a health care provider’s recommendations if they trust and have a good relationship with that provider (Bennett, 2010, p. 8-9). The process of recording a medical and family history puts the patient in the role of expert, which may promote empowerment, better listening and decrease anxiety (McCarthy et al., 2003; Erlanger, 1990; Rogers and Durkin, 1984; and Rose et al., 1999).

Genetics clinics can be general or they can specialize in a particular type of disorder. Examples include hereditary cancer syndromes, Huntington’s disease, muscular dystrophy and pediatric cancer. Oftentimes genetics will be part of a multidisciplinary clinic with other specialties, including oncology, neurology, endocrinology or ophthalmology. Patients may have clinical evaluations with a geneticist, a genetic counselor, or both (Murray & Jain, 2015).
IV. Where we are today: Benefits, challenges and opportunities surrounding genomic medicine in rare disease

When a clinical genetics evaluation suggests an underlying genetic condition may be present, testing is often ordered to confirm a suspected diagnosis. This testing can include imaging, biochemical testing and genetic testing, among other clinical evaluations. Clinical geneticists and genetic counselors make a judgment on the right strategy for testing based on several factors, which can include medical purpose (e.g., kind of disorder, family history), technical considerations and costs (Strande & Berg, 2016). Genetic sequencing tests are frequently ordered in the clinical setting when rare, genetic disease is suspected. These can include: single-gene tests using NGS to sequence a gene, which often includes deletion/duplication analysis, as well; panel testing, which utilizes these same approaches but analyzes multiple genes at once; “site-specific” testing looking only at a specific variant that has previously been identified in a family; whole exome sequencing, which utilizes NGS approaches across the entire coding region of the genome – the exons; and whole genome sequencing, which is a comprehensive analysis of the genome. Since it has been estimated that, at most, 46% of patients presenting to medical genetics specialists and suspected of having a genetic disorder are currently diagnosed using traditional genetic diagnostic evaluations, comprehensive clinical evaluations, targeted genetic testing, and chromosomal copy number analyses, approaches for improving diagnostic rates are still needed. In many instances, NGS is helping fill this diagnostic gap (Shashi et al., 2014).

There are many benefits to genetic testing for the individual patient; first and foremost, molecular confirmation of a diagnosis that is suspected clinically. This occurs when
a genetic test returns a “pathogenic” (disease-causing) or "likely pathogenic” variant. As Wise et al. (2019) note, diagnoses derived from genetics evaluations and testing offer: new opportunities for therapeutic intervention and condition specific management; family planning; cascade testing of family members; justification for social and educational services; and the opportunity to connect with other individuals and families affected by the same condition. Receiving a diagnosis has also been shown to confer other benefits such as increasing knowledge, providing a sense of empowerment, increasing parental quality of life, decreasing parental guilt and promoting increased acceptance (Savatt & Myers, 2021).

Recent studies examining the diagnostic setting have shown exome sequencing to be the most comprehensive and cost-effective method to rapidly detect the underlying etiology in patients with genetic disease (Gomez & Das, 2014; Monroe et al., 2016; Soden et al., 2014; Stark et al., 2017; Tan et al., 2017; Vissers et al., 2017). Single-gene and panel testing are most frequently used when a particular gene or group of genes are strongly suspected based on a patient’s clinical phenotype, while exome and genome sequencing tend to be used when the clinical picture is less clear (Manolio et al., 2015). There are certain clinical scenarios and conditions for which sequencing analysis is not an appropriate testing strategy and clinicians will opt for other types of genetic tests. Examples include: chromosomal microarray, a type of genetic testing that examines amounts of chromosome material and is typically the first test ordered when phenotype includes developmental delay/intellectual disability; DNA methylation analysis, a type of testing that looks at chromosomal patterns of DNA or histone modification by methyl groups and can detect parental-specific imprinting in Prader-Willi and Angelman syndromes; and PCR analysis, which is used to diagnose repeat expansion disorders such as Huntington disease. Regardless of the genetic testing approach selected, it
is imperative for the clinical genetics team to provide detailed phenotypic information on the patient to the laboratory; this context is critical in proper test interpretation and ultimately aids in diagnosis.

Additionally, inborn errors of metabolism and mitochondrial disorders often have hallmark biochemical test findings, so when these are suspected, that type of testing may be the first order. Clinical criteria for diagnosis of certain genetic conditions such as Marfan syndrome also require imaging such as an electrocardiogram of the heart. Depending on the patient’s pathway to genetics, other specialists may have ordered any of these types of tests, or it may be up to the clinical geneticist to do so.

ACMG recommends that exome or genome sequencing be considered in the clinical diagnostic assessment of a phenotypically affected individual when: no single gene or panel tests are available; a patient presents with a defined genetic disorder that demonstrates a high degree of genetic heterogeneity, or in other words, when there are too many genes to test; or previous genetic testing available for the phenotype has been uninformative (ACMG Board of Directors, 2012). Advantages of genome sequencing compared to exome are that it provides more coverage, better resolution of structural variants such as insertions and deletions and a faster output of data. It also provides a means to analyze non-coding variants. However, genome has not yet been widely adopted in clinical practice. It is typically more expensive, in part due to the fact that the substantially more data produced require more time for analysis. Another type of testing on the horizon yet not currently widely used clinically is RNA-seq/transcriptome analysis, which examines RNA transcripts to detect non-
coding variants, and examines the coding genome, particularly to detect altered splicing of transcripts generated (Manolio et al., 2015).

Published studies have shown that the diagnostic rate for NGS is upwards of 25%, with multiple studies showing the yield for exome sequencing in particular ranges from 25-35% (Farwell et al., 2015; Farwell et al., 2017; Gahl et al., 2012; Iglesias et al., 2014; Lee et al., 2014; Retterer et al., 2016; Srivastava et al., 2014; Yang et al., 2013; Yang et al., 2014). This rate is two to three times as likely as traditional methods to diagnose a genetic disease (Gomez & Das, 2014; Monroe et al., 2016; Shashi et al., 2014; Stark et al., 2017; Vissers et al., 2017). It is expected this rate will continue to grow as gene discovery advances.

On the opposite end of the spectrum from a molecular diagnosis, a patient may receive a “benign” or “likely benign” result on a genomic test, indicating a variant in a gene known to be associated with a given condition was not identified. These are considered negative results.

Beyond a positive or negative, however, genetic tests can deliver a third type of result, a variant of uncertain significance (VUS), and this can be a challenge for health care providers and patients alike. A VUS result signifies that a variant was identified, but there is not sufficient data to classify it as pathogenic, likely pathogenic, likely benign, or benign, or available evidence is conflicting. There is consensus in the genetics specialty that, by and large, medical management and surgical decisions should not be made on the basis of an identified VUS, and familial and prenatal testing are not offered for VUSs (Richards et al., 2015). However, as Ackerman describes, receiving this type of result can place health care providers and patients in a “genetics purgatory,” where they are stuck in a place of potential
misery and suffering, including uncertainty and potential for radical treatment recommendations to be made based on the presence or absence of a “maybe mutation.” (Ackerman, 2015). Patients and even health care providers may misinterpret the meaning of VUS, leading to anxiety or unnecessary testing or treatment. Most often, VUSs are reclassified as benign, but some are eventually found to be associated with disease or risk for disease, underscoring the importance of the genetics care team monitoring for new classifications over time (Slavin et al., 2019). Part of the role of clinical geneticists and genetic counselors is to liaise with laboratories regarding patients’ VUSs, to obtain pertinent reclassifications, and ensure updates are communicated and management plans adjusted accordingly. Genetic counselors have expressed that result interpretation and disclosure of incidental findings and VUSs has been a challenge related to offering NGS-based testing (Machini et al., 2014).

Establishing a diagnosis that has eluded a patient and their care team for many years has been the focus of several public programs. The NIH Undiagnosed Diseases Program, founded in 2008, and Undiagnosed Diseases Network, founded in 2013, have reported successes with arriving at diagnoses for patients with complex phenotypes and combinations of complex phenotypes, as well as in identifying insights on disease pathogenesis. These successes led to the creation of the global Undiagnosed Diseases Network International, which is now operating in 15 countries (Undiagnosed Diseases Network International, 2021). Another effort, the International Rare Diseases Research Consortium, was officially launched in 2011 with the goal of contributing to the development of 200 new therapies and means to diagnose most rare diseases by 2020, and achieved its therapy milestone by 2017. It has since set a global rare disease goal for 2017-2027 of “enabling all people living with a rare disease to receive an accurate diagnosis, care and
available therapy within one year of coming to medical attention.” Progress in genomics has been a common thread enabling the successes of these efforts.

Another significant benefit of genomic medicine is that it has enabled progress for treatment of those who receive a genetic diagnosis. As Arnold (2018) points out, the “inborn errors of metabolism” – metabolic conditions – offer a good example of how treatment for genetic conditions has evolved over the 20th and 21st centuries. Early approaches (some of which are still important strategies today) focused on reducing the abnormal metabolites, for example, through dietary restriction of phenylalanine and supplementation of the deficient end product, tyrosine, in phenylketonuria (PKU). Treatment strategies then shifted more directly to correcting the underlying metabolic defect, such as through liver and stem cell bone marrow transplantation, chaperonins to optimize protein folding, enzyme replacement therapies, therapeutic mRNA and microbiome alteration. Today, excitement is high for the promise of genetically targeted therapies and gene therapy (Arnold, 2018).

The concept behind gene therapy is that the introduction, removal or change of genetic material in the cells of a patient can change how proteins are produced, thus targeting the underlying genetic cause of disease. Approaches include introducing a new gene or correcting or “editing” an existing gene. Genetically targeted therapies, on the other hand, such as antisense oligonucleotides (ASOs) and small interfering RNAs (siRNAs) work by silencing gene expression. Gene therapy and gene correction techniques have been explored in Mendelian disorders as well as several cancers, and four therapies have reached U.S. Food and Drug Administration and/or European Medicines Agency approval for clinical use (Rao et al, 2018).
Taking spinal muscular atrophy, a rare genetic disease affecting motor nerve cells in the spinal cord caused by variants in SMN1 as an example, two therapies, AVXS-101 and nusinersen, have been approved and shown to improve the lives of people living with the condition. AVXS-101 delivers a copy of the gene whereas nusinersen uses an SMN2-directed ASO technology to make the protein produced by SMN1’s “back-up” gene, SMN2, functional. As of 2019, there were more than 1,000 clinical trials for gene therapies, cell therapies and tissue engineering products and more than 4,500 people in the United States and Europe had been treated with approved gene therapies and gene-modified therapies such as CAR-T cancer treatments (Alliance for Regenerative Medicine, 2019). However, barriers to widespread adoption of these and other gene therapies include safety concerns, high cost and access (Rao et al., 2018; Chen, 2020).

The American public has consistently been shown to have positive views toward genetics research and optimistic view of its potential to improve human health through prevention of disease and risk detection and reduction (American Society of Human Genetics [ASHG], 2020). Patients believe genetic testing has psychosocial benefits in addition to medical ones. For example, a 2013 study by McGowan et al. showed that patients reported beliefs that: having access to more comprehensive information on one’s personal genetic health risks was better than less knowledge; knowing one’s genetic health risks would improve quality of life and bring peace of mind; having genetic testing would facilitate planning and decision-making for future health care; and getting testing results could facilitate communication between family members about shared disease risks. Parents interviewed in the study also explained that having a diagnosis allowed them to feel they were treating it in a better way. Conversely, patients have expressed concerns about the
emotional burden that genetic testing information may present, genetic privacy, and the possibility for discrimination based on results (ASHG, 2020; McGowan et al., 2013).

Many physicians express enthusiasm for genetic testing. Surveys show they are optimistic that genomic medicine will increasingly become a part of clinical care, especially as it relates to surveillance and medication selection. However, these studies have also highlighted limitations in physician understanding of genetics and genomic testing and concerns over privacy and discrimination (Manolio et al., 2015; Raghavan & Vassy, 2014).

From a societal point of view, genomic medicine has the potential benefit of significantly reducing health care economic burden. By shifting emphasis from therapeutic intervention to prevention, genomic medicine has the potential to help reduce morbidity, avoid “trial and error” medication strategies, reduce unnecessary side effects of medications and save costs for the individual and society (Manolio et al., 2013; Vozikis et al., 2016).

Another societal benefit of genomic medicine is the data sharing that it has enabled. Data sharing has helped advance scientific understanding of variants and clinical characteristics associated with disease-causing variants, and has the goal of ultimately improving genetics care for future patients. Through resources such as ClinGen’s GenomeConnect, NHGRI’s MyGene2 and Baylor-Hopkins Centers for Mendelian Genomics’ GeneMatcher, patients and clinicians are able to upload their personal genetic and clinical information in the hopes that it may be useful to others, for diagnosis or research efforts (Manolio et al., 2015).

Access issues have often been cited as a key barrier to genomic medicine optimization. Genomic medicine suffers from the access and outcomes disparities that
plague the health care system generally (such as with underinsurance and worse outcomes among racial minorities and those of lower socioeconomic status), but there are also several issues unique to the space. First, there are a limited number of trained genetics professionals. Most work in academic medical centers, and on average in the United States, there are 1 to 1.5 genetics professionals per 100,000 residents. These professionals are concentrated on the West Coast and in the Northeast. Just under half (49%) of genetic counselors work in ten U.S. states: California, New York, Pennsylvania, Texas, Ohio, Massachusetts, Illinois, Michigan, North Carolina, and Minnesota (NSGC Professional Status Survey, 2021). As genomic medicine science advances and public demand continues to grow, it is likely that there will be an increased need for genetics professionals. Second, utilization of available genomic tests varies among demographic groups, for several possible reasons, including confidence in tests, practice linkages with specialty care, patient awareness and willingness to undergo testing, racism and discrimination and low prioritization for patient populations with significant comorbidities and complex health issues (Institute of Medicine, 2009). Country-specific differences have also been shown to exist, such as in a study examining genetic counseling and testing for breast cancer in Australia, Canada, France, Germany, Netherlands, the UK and the U.S. that found differences in provider and patient attitudes to genetic counseling and genetic testing; utilization rates of genetic testing and prophylactic surgery; and the psychological impact of genetic testing for breast cancer risk (Meiser et al., 2006). Studies have also identified challenges with genetic counseling when performed in minority populations with different cultural attitudes about authority and patient autonomy; for example, a study conducted on the
Arab population in Israel showed miscommunication led to uncertainty, frustration and distrust (Cohen-Kfir, et al., 2020).

Additionally, while the NIH notes that genetic testing is typically reimbursed when deemed medically necessary by a health care provider, reimbursement for genetics services varies widely. Insurers may have difficulty evaluating what type of test was performed and whether it is scientifically valid, due to lack of sufficient codes in the standardized Current Procedural Terminology (CPT) system developed by the American Medical Association, which governs how procedures are billed. There is also a lack of extensive data evaluating the economics of genetic testing, driven in part by the explosive growth of testing (NIH NHGRI Coverage and Reimbursement of Genetic Tests, 2019). Finally, there is currently lack of sufficient infrastructure to support the informatics demands of integrating genomic information into electronic medical records (EMRs) and the clinical workflow (Manolio et al., 2019).

Another significant barrier to future genetic discovery and genomic medicine implementation is that genome-wide association studies (GWASs) have historically focused primarily on populations of European descent from very few countries, primarily the United States, the United Kingdom and Iceland. This means genetic variants in people of other ancestries can be missed entirely or misunderstood. There is widespread acknowledgement of the need to diversify studied populations to improve the effectiveness of current testing technologies and advance understanding of disease etiology (Peterson et al., 2019). This barrier has recently been the topic of much discussion as research efforts, and some clinicians, have begun to integrate polygenic risk scores into their toolkits when assessing
risk for common, multifactorial conditions (those determined by multiple genetic, epigenetic and environmental factors). A polygenic risk score reveals how a person’s risk compares to others with a different genetic constitution. Because they rely on GWAS data, these scores have come under scrutiny, with many in the genetics and genomics community advocating against their implementation until more patients can benefit (Lewis & Green, 2021; NIH NHGRI Polygenic risk scores, 2020).

V. Where we are today: Integrating genomic medicine into clinical care

While genomic medicine clearly has its benefits, there is still much work to be done. From a timing point of view, this is not surprising. It has been estimated that it takes 17 years on average to translate a new research finding into clinical care (Balas & Boren, 2000; Institute of Medicine, 2001; Morris et al., 2011; NIH NHGRI Genomics and medicine, 2020).

Integrating genomic medicine into clinical care can be thought of on both micro (focusing on the tests themselves) and macro (focusing on the genomics/genetics community’s process) levels. Starting with the micro, Burke et al. (2007) described the introduction of new genetic tests as a three-step process: a new test is proposed for clinical use based on research findings; the health care value of that test is then evaluated, either formally or informally; and then decisions and judgments are made regarding the clinical use and reimbursement of the test. They noted that this process mirrors that of any medical innovation introduction.

Manolio et al. (2019) proposed a spectrum model to describe the journey the genetics and genomics community has been on since the time of the HGP, starting with discovery research, progressing to clinical validation and then finally achieving clinical implementation. In the discovery research phase, genotype-phenotype associations are
assessed. This can include identifying people at increased risk of disease based on genomic variants and characterizing variation and function of genes known to be related to disease. This stage is followed by clinical validation, in which outcomes are assessed after using genomic testing results to direct therapy. Here, the impact of genomic information on health outcomes and care utilization for patients, families, providers and health care systems, also known as clinical utility, is assessed. Finally, processes for performing genomic testing are developed, and providers begin using results in clinical care. This phase includes educating physicians and patients about the use of genomic results and developing clinical informatics systems for reporting genomic results.

VI. Defining the clinical utility of genomic medicine

The “clinical validation” step in Manolio et al.’s model (2019) requires demonstration of clinical utility of genomic medicine. Clinical utility is also a critical measure underpinning policymaker and payer requests for evidence on the value of genomic medicine (Hayeems et al., 2020). Clinical utility can broadly refer to the use of test results to inform clinical decision-making. A test does not itself have inherent utility; rather, it spurs the adoption of associated therapeutic or preventive interventions that influence health outcomes (Grosse & Khoury, 2006). In genomic medicine in particular, according to ACMG’s 2015 position statement on “Clinical utility of genetic and genomic services,” “clinical utility refers to the likelihood that a given intervention (in this case, genetic information) will lead to an improved health outcome or to whether a test can provide information about diagnosis, treatment, management, or prevention of a disease that will be helpful to a consumer” (ACMG Board of Directors, 2015). ACMG submits that clinical utility of genetic testing and services should take into account effects on diagnostic or therapeutic management, implications for
prognosis, health and psychological benefits to patients and their relatives, as well as economic impact on health-care systems. In other words, the value of a genetics diagnosis extends beyond the individual to the family and society in general.

VII. Working toward clinical utility and implementation

Despite widespread recognition that demonstration of clinical validity is key in advancing the promise of genomic medicine, there is not currently a single, validated measure to quantify clinical utility in genomic medicine. As Hayeems et al. (2015) point out, part of the challenge lies in the fact that traditional measures of clinical effectiveness reflect final outcomes such as life years gained or preference-based measures, such as quality-adjusted life years. Genetic testing effectiveness must acknowledge a different outcome, earlier in the process: usefulness to patient management decision-making. Hayeems et al. (2020) have proposed a clinician-reported measure of clinical utility for genetic testing, Clinician-reported Genetic testing Utility InDEx (C-GUIDE), and work continues to establish its inter/intrarater reliability and construct validity in a range of clinical settings with a range of provider types.

In the meantime, a robust evidence base of clinical utility is emerging in the pediatric setting, with multiple studies demonstrating significant diagnostic yield of chromosomal microarray and exome sequencing in neurodevelopmental disorders and intellectual disability, and linking chromosomal microarray results to altered medical management (Coulter et al., 2011; Henderson et al., 2014; Monroe et al., 2016; Riggs et al., 2014; Savatt & Myers, 2021; Srivastava et al., 2019; Vissers et al., 2017). Studies are emerging on the utility of genome sequencing as well, such as Sanford et al. (2019), which demonstrated that rapid genome sequencing has clinical utility in the PICU specifically, and Soden et al. (2014) which
showed that if children with neurodevelopmental disorders had received exome or genome sequencing at symptom onset, genomic diagnoses may have come years earlier. However, as Hayeems et al. describe, existing pediatric setting studies have been limited by reliance on data reflecting hypothetical clinical scenarios, lack of comparison groups, limited consideration of variants of uncertain significance or insufficient consideration of the factors beyond the testing result itself that contribute to medical management in the context of pediatric genetics (2015).

Large health systems are beginning to investigate the issue of genomic medicine clinical utility, such as a 2017 study of Veterans Affairs clinical leadership. The study found that tests that inform clinical management had the highest value rating (58.6%), followed by reproductive options (50.1%), life planning (43.9%), and a suspected (39.9%) or established (32.3%) diagnosis. Study authors posited that engaging leadership on understanding reasons for genetic testing and its value beyond clinical utility may increase adoption (Lerner et al., 2017).

Several large-scale efforts in the United States and beyond, including NHGRI’s All of Us Research Program, Implementing Genomics in Practice (IGNITE) and Clinical Sequencing Evidence-Generating Research (CSER) Consortium, Australian Genomics and the UK’s 100,000 Genomes Project, have aimed and continue to aim to address genomic medicine implementation barriers, expand the clinical utility evidence pool and move systems more fully to the clinical implementation end of the gene-disease research and implementation spectrum. Private health systems have also embarked on large-scale sequencing efforts aimed at improved drug discovery and clinical care (Amendola et al., 2018; Manolio et al., 2013; Stark et al., 2019).
VIII. Gaps in current knowledge and research

As described, there are several gaps in current research efforts examining clinical utility of genomic medicine. There is a need for more research on the clinical utility of genomic medicine. Where studies do exist, they tend to center on a limited range of disorders in pediatric populations or in cancer in adults; clinical utility across a broader spectrum of disease, particularly among adults remains unclear (Lata et al., 2018). Additionally, these studies tend to focus on diagnostic yield for the individual. In line with ACMG’s call for an expanded view on clinical utility, there is a need for more studies looking at what genetics provides in addition to testing results, for the individual, as well as their family and society on the whole. Further, in light of the genetic counseling community’s excitement about how their training in providing patient education may be an asset in the implementation of precision medicine approaches (both directly and through the training of others; Wicklund et al., 2018), more study is needed about the role the counseling process is currently playing, to identify future barriers and opportunities.

IX. Purpose and aims of the study

Conducting a retrospective chart review of new patients seen at the UC Irvine Medical Center (UCIMC) Adult Genetics clinic offers the opportunity to gather real-world evidence on what is occurring in a general genetics clinic that provides services to a diverse patient population (ethnically and socioeconomically), as well as to observe any barriers that may exist. Given that the study period covers the COVID-19 pandemic, it also provides a unique opportunity to gather evidence on telemedicine visits. The aim of this study is to explore evidence for utility of genomic medicine approaches for individuals, families and society. To accomplish this aim the study will i) describe characteristics of patients referred to genetics
clinic, including examining referral type, number of specialists seen and indication for testing and ii) characterize what genetics provides those patients, including documenting when detailed physical exams occur and examining type of testing and patient follow-through on ordered testing, diagnostic yield and type, time to diagnosis, test turnaround time, referrals placed and counseling components provided. The study also will investigate whether any statistically significant differences exist in what genetics is providing based on: whether a diagnosis was obtained; ancestry; insurance type and whether the evaluation occurred in person (prior to the COVID-19 pandemic) or via telemedicine (during the pandemic).

While a diagnosis is inherently valuable, there are other components of the genetics interaction known anecdotally to be perceived as valuable, as well. These include education on the prognosis of the condition and inheritance patterns, new surveillance recommendations for the individual and that information provided to their primary care physician (PCP), family planning guidance, and the opportunities to access support resources, which may enable connecting with other individuals affected by a similar constellation of symptoms, as well as to help advance research. It is therefore hypothesized that the genetics interaction will offer takeaways that could be perceived as valuable regardless of whether a diagnosis is obtained. Given the high costs and rapidly evolving technologies associated with genomic testing, it is hypothesized that the insurance reimbursement process may be a barrier to test completion. Secondly, knowing that current genetic analyses center on data from individuals of European ancestry, it is hypothesized that non-European ancestry could be a barrier to obtaining a diagnosis. It is also hypothesized that the telemedicine work-flow – in which a patient first attends a visit remotely and then may be required to present to a laboratory to provide a testing sample at
a different time – may be a barrier to test completion and diagnosis (given delays at the laboratory and clinic scheduling end), but that there will be no difference in the counseling components provided. The information obtained in this study will provide essential data that can help inform ongoing efforts surrounding implementation of genomic medicine approaches.

METHODS

I. IRB approval

This study was approved by the University of California, Irvine (UCI) Institutional Review Board (IRB) under study HS# 2020-6299.

II. Retrospective chart review

The study was a review of charts of new, adult patients – aged 18 and older – seen at UCIMC sites (Pavilion I, Plaza and telemedicine). Both self-referrals and physician referrals were included. All patients first evaluated by genetics during the period of January 1, 2019 through IRB approval date, December 10, 2020, were included. Testing and follow-up consultations that occurred between December 10, 2020 and April 17, 2021 were included, provided that the patient was first seen on or before December 10, 2020. Using the secure electronic database of UCIMC Genetics patients, patients were first identified for inclusion by date seen. To keep subject identifiers separate from the research information, a code was created, linking the patient medical record numbers with newly generated non-identifying patient numbers. The coded data were stored on a UCI network computer within the secured Health Sciences network in the City Tower, Suite 800 Department of Pediatrics and at Hewitt Hall on UCI Main Campus, and the code key was stored in a separate, secure file on a UCI
network computer within the secured Health Sciences network. No hard copies of coded data were collected.

A total of 118 patients met inclusion criteria. Patients were excluded if: they were under 18; they never attended the first visit; clinical documentation was unavailable or incomplete; they were attending a specialty or other genetics clinics (e.g., Fabry disease, cancer counseling, prenatal counseling); they were return patients; or their records were duplicates. The lead author reviewed the patient referrals and clinical documentation, and collected data onto a data collection sheet that was used for subsequent analysis.

Patient demographics such as age, gender, zip code, date seen, race/ethnicity, preferred language and insurance type (HMO, EPO, PPO, Medicaid/Medicare/Tricare) were collected.

From clinical documentation, information was collected regarding what was available when the patient came to genetics and what genetics provided for the individual patient, their family and society (see Appendix A). Only documentation of visits to genetics was examined; other providers’ documentation was not reviewed.

Ten patient charts (9%) randomly selected from across the study period (January 1, 2019 to December 10, 2020) were re-analyzed for all 72 variables. Charts initially analyzed were compared to these re-analyzed charts and a data collection error rate of 1% (10 out of 720) was determined.

III. Data analysis

To analyze the data, the lead author used the IBM Statistical Package for the Social Sciences (SPSS) Statistics version 25 (IBM SPSS Statistics for Macintosh, Armonk, NY, USA, IBM Corp). Descriptive analyses were used for patient demographics, referral features,
genetics exam features and genetics recommendations, including summarizing using means and standard deviations for continuous variables and counts and percentages for categorical variables. To analyze the measures of clinical utility for the individual, family and society, bivariate comparisons (chi-square tests for categorical variables, t-tests for continuous variables) were calculated using SPSS. P-values <0.05 were considered statistically significant. Nominal p-values are reported; no correction was made for multiple comparisons.

RESULTS

1. Records reviewed

Of the 118 records meeting inclusion criteria, the year seen was distributed as follows: 2020 (54; 46%) and 2019 (64; 54%). Seventy-four (63%) of these first visits were in-person visits, whereas 44 (37%) were via telemedicine (Table 1). Of the telemedicine visits, 36 (82%) were via video and audio, while 8 (18%) were audio only.

Table 1. Number of patients by year and mode

<table>
<thead>
<tr>
<th>Year</th>
<th>Referrals That Met Criteria</th>
<th>In Person</th>
<th>Telemedicine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Referrals N=163</td>
<td>N=118</td>
<td>N=74</td>
</tr>
<tr>
<td>2019</td>
<td>78</td>
<td>64</td>
<td>64</td>
</tr>
<tr>
<td>2020</td>
<td>85</td>
<td>54</td>
<td>10</td>
</tr>
</tbody>
</table>
II. Demographics and referral information

The demographic characteristics of the 118 patients were analyzed (Tables 2 and 3). Types of insurance reported were categorized into: private, which included HMO, EPO and PPO; government, which included Medicare, Medicaid and Tricare; and self pay. Five patients’ race/ethnicity was missing from documentation. The majority of patients were female (64%), White (61%) and had private insurance (56%). The age of the patients ranged from 18-78 years with a mean age of 41.4 years.
Table 2. Age, Gender and Insurance Type

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=118</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Range)</td>
<td>18-78</td>
</tr>
<tr>
<td>Age (Mean/Standard Deviation)</td>
<td>41.4/15.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-27</td>
<td>24</td>
<td>20</td>
</tr>
<tr>
<td>28-37</td>
<td>31</td>
<td>26</td>
</tr>
<tr>
<td>38-47</td>
<td>26</td>
<td>22</td>
</tr>
<tr>
<td>48-57</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>58-67</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>68-77</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>78-87</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gender</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>76</td>
</tr>
<tr>
<td>Male</td>
<td>42</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Insurance type</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Private</td>
<td>66</td>
</tr>
<tr>
<td>Government</td>
<td>52</td>
</tr>
<tr>
<td>Self-pay</td>
<td>0</td>
</tr>
</tbody>
</table>
Table 3. Race/Ethnicity

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>69</td>
<td>61</td>
</tr>
<tr>
<td>More than 1</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>Asian or Pacific Islander</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Hispanic</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Black</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Native American or Alaska Native</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*N=113*

*Race/ethnicity documentation was available for 113 of the 118 patients in the study.

One hundred fourteen (97%) of the patients were referred by physicians, while 4 (3%) were self-referrals.

The reasons for referral were categorized (Figure 1). The main reason for referral was suspicion of a genetic condition diagnosis (65% of patients), followed by family history of confirmed or suspected genetic condition diagnosis (13%) and referral to discuss previous genetic testing results (11%). Eleven percent of referrals were for more than one reason. Suspicion of a genetic condition diagnosis was based on physician evaluation and/or patient input.
Figure 1. Reasons for referral.

Reasons for referral for the 118 patients in the study were categorized. The most common referral reasons with suspicion of a genetic condition diagnosis (65%; based on physician evaluation and/or patient input), followed by family history of confirmed or suspected genetic condition diagnosis (13%) and referral to discuss previous genetic testing results (11%). Eleven percent of referrals were for more than one reason (11%).

III. Diagnosis rate

Of the 118 patients receiving a genetics evaluation, 94 (80%) saw a physician and a genetic counselor, while 24 (20%) saw only a genetic counselor. Eighty-five (72%) received a physical examination while 33 (28%) did not. Eighty-six (73%) were assessed to have a presentation suspicious for a genetic condition. Nine of these patients (11%) received a clinical diagnosis of a genetic condition, using clinical criteria. At least one genomic test was
recommended for 73 of the 86 patients (85%), and of these, 47 patients (64%) went on to have genomic testing. Genomic testing was defined as tests focused on gene sequencing (including single-gene, panel, pharmacogenomic, exome and genome testing) or those using cytogenetic methods (including karyotype, chromosomal microarray and fluorescence in situ hybridization [FISH] analysis) to analyze genetic information.

Of the 47 who had genomic testing, 17 patients (36%) were given a molecular diagnosis. Diagnosis was defined as a positive result on a genetic test, evaluated as such by the clinician and laboratory. Of these 17, 15 were genetic diagnoses for the individual while 2 were positive carrier results, indicating the individual was not affected with a genetic condition but future children could be at risk of developing the condition. The remaining 30 (64%) were believed to have a presentation consistent with a genetic disorder but remained undiagnosed after genomic testing.

The indications for testing in the 47 individuals who had testing were grouped into the following categories (Figure 2): bleeding disorder (2; 4%); cancer (1; 2%); cardiomyopathy (1; 2%); chromosomal condition (2; 4%); connective tissue disorder (7; 15%); dermatologic condition (3; 6%); disorder of sex development (1; 2%); drug sensitivity (1; 2%); kidney disorder (1; 2%); metabolic disorder (4; 9%); mitochondrial disorder (1; 2%); myopathy (2; 4%); neurodegenerative disorder (8; 17%); ophthalmologic condition (4; 9%); skeletal dysplasia (4; 9%); carrier testing (2; 4%); and other (3; 6%). Of note, ophthalmologic condition testing indication was based on prior specialized ophthalmologic examination/referral to genetics; this physical evaluation was not conducted by the genetics team.
Figure 2. Testing indications.

Indications for testing in the 47 individuals who had tested were grouped into categories. The most frequent indication was neurodegenerative disorder (17%) followed by connective tissue disorder (15%) and skeletal dysplasia, ophthalmologic condition and metabolic condition (9% each).

Diagnostic yield was highest for cancer, carrier testing, mitochondrial disorders and ophthalmologic conditions (Table 4). It should be noted, however, that the sample size for some of these categories is quite small.
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Patients diagnosed</th>
<th>Patients tested</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding disorder</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Cancer</td>
<td>1</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Chromosomal condition</td>
<td>1</td>
<td>2</td>
<td>50</td>
</tr>
<tr>
<td>Connective tissue disorder</td>
<td>0</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Dermatologic condition</td>
<td>1</td>
<td>3</td>
<td>33</td>
</tr>
<tr>
<td>Disorder of sex development</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Drug sensitivity</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Kidney disorder</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Metabolic disorder</td>
<td>2</td>
<td>4</td>
<td>50</td>
</tr>
<tr>
<td>Mitochondrial disorder</td>
<td>1</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>Myopathy</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Neurodegenerative disorder</td>
<td>4</td>
<td>8</td>
<td>50</td>
</tr>
<tr>
<td>Ophthalmologic condition</td>
<td>4</td>
<td>4</td>
<td>100</td>
</tr>
<tr>
<td>Skeletal dysplasia</td>
<td>0</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>3</td>
<td>33</td>
</tr>
<tr>
<td>Carrier testing</td>
<td>2</td>
<td>2</td>
<td>100</td>
</tr>
</tbody>
</table>
Forty-four of the 47 patients who had genomic testing had ancestry information available for analysis. Of these, 31 had European ancestry – defined as patients’ having named one or more countries in Europe during pedigree collection – and 13 did not have European ancestry. Significantly more people who did not have European ancestry were diagnosed via genomic testing than those who did, 69% versus 26% (N=44; Pearson Chi-square value = 7.285, p < 0.007). See Figure 3.
Figure 3. Diagnosis by European ancestry reported in pedigree.

Of the 47 patients who completed genomic testing, 31 were of European ancestry and 13 were not. European ancestry was defined as reporting at least one country in Europe during pedigree collection. For three patients, ancestry information was not available. Significantly more patients who were not of European ancestry were diagnosed via genomic testing than those who were (69% versus 26%, respectively; N=44; Pearson Chi-square value = 7.285, p < 0.007).

IV. Diagnosis type

The 17 conditions diagnosed after genomic testing were grouped into the following categories: single-gene disorders (88%); chromosomal conditions (6%); and mitochondrial disorders (6%). The 15 single-gene disorder diagnoses were categorized. The majority were ophthalmologic (27%) and neurodegenerative (27%; Figure 4).
Figure 4. Single-gene disorders diagnosed.

Fifteen single-gene disorders were diagnosed via genomic testing in the study. These disorders were grouped. Ophthalmologic conditions and neurodegenerative disorders were the two most common (27% each), followed by metabolic disorders and other (13% each). Bleeding disorders, dermatologic conditions and heritable cancer syndromes contributed the fewest patients.

For the 9 patients who received a clinical diagnosis, disorder categories included: connective tissue disorder (7 patients; 78%); metabolic condition (1 patient; 11%); and heritable cancer syndrome (1 patient; 11%). Genetic testing was recommended for 1 of the 9 patients (11%) receiving a clinical diagnosis – the patient receiving a clinical cancer diagnosis – but this test was not completed. The 7 connective tissue disorder patients
included 3 diagnosed with hypermobile Ehlers-Danlos syndrome (formerly known as Ehlers-Danlos syndrome type III) and 4 diagnosed with hypermobility spectrum disorders.

V. Number of specialists seen prior to genetics and time to evaluation

The mean number of specialists seen prior to genetics by the 118 patients evaluated by genetics was 2.9. The range of specialists seen was 0 to 16 and the standard deviation was 2.5. Number of specialists seen prior to genetics data were available for 41 of the 47 patients completing genomic testing. The mean number of specialists seen by patients who remained undiagnosed (N=25) after genomic testing, 3.00, was significantly higher than the mean number seen by the diagnosed patients, 1.38 (N=16; t=3.026; p<.0004; Figure 5).

Figure 5. Number of specialists seen by diagnosis status.

People who remained undiagnosed following genomic testing (N=25) saw more specialists prior to the genetics clinic than those who were diagnosed (N=16; t=3.026; p<.0004). In these box plots, the boxes extend from the first quartile to the third quartile. Vertical lines go through the boxes at the median. The whiskers go from each quartile to the minimum or maximum.
Overall, the mean time from initial symptom presentation to genetics evaluation for the 118 patients evaluated was 15.6 years. There was not a statistically significant difference in mean time from initial symptom presentation to genetics evaluation for the two groups; the mean time for the genetic diagnosis group with data available (N=14) was 18.8 years, while the undiagnosed group with data available (N=25) had a mean time of 17.4 years (t = -0.233; p<0.817).

**VI. Types of testing ordered and follow-through**

Forty-seven of the 73 patients for whom genomic testing was ordered followed through on their testing. Significantly more patients in the in-person group (N=47) followed through on their testing (77%) than in the telemedicine group (N=26; 42%; Pearson Chi-square = 8.582; p<0.003). See Figure 6.
Seventy-three patients were recommended to have genomic testing. 47 of these were seen in-person and 26 were seen via telemedicine. Significantly more patients in the in-person group followed through on their testing (77%) than in the telemedicine group (42%; Pearson Chi-square = 8.582; p<0.003).

Roughly equivalent percentages of people with private insurance (62%) and government insurance (67%) followed through on their genomic testing; this difference was not statistically significant (Pearson Chi-square = 0.190; p<0.663).

Of the 47 patients who went on to have testing, a total of 70 tests were ordered. These included 55 genomic tests, 6 biochemical tests, 5 imaging studies, 2 enzyme tests and 2 other. Of the 55 genomic tests, 29 were panel tests, 14 were single gene, 4 were karyotypes, 4 were microarrays, 2 were exome sequencing, 1 was pharmacogenetic and 1 was a FISH study. NGS was the overwhelming contributor to diagnosis – accounting for 16 of the 17 diagnoses in the study. The other diagnosed patient in the study received their diagnosis via karyotype.
Of the 44 patients receiving at least one NGS test, defined as single-gene, panel tests, exome sequencing and pharmacogenomic testing, results for 42 were available for analysis.

Sixteen (38%) received a molecular diagnosis (a positive test result defined as pathogenic or likely pathogenic variant[s] identified). Sixteen patients (38%) received a negative result – defined as no variant identified – on their NGS test. Ten (24%) patients received at least one VUS on an NGS test. The types of genetic tests used were categorized based on patient diagnosis type (Figure 7).

![Figure 7. Genomic tests utilized by patient diagnosis type.](image)

One hundred percent of the chromosomal conditions diagnoses (1) were achieved through karyotype analysis. One hundred percent of the mitochondrial disorder diagnoses (1) were achieved through single-gene tests. The single-gene disorders were primarily diagnosed by panel tests (12; 80%), followed by single-gene tests (2; 13%) and exome sequencing (1; 7%).

Data on turnaround time – the time from appointment to results return to the patient – were available for 44 of the 47 patients who completed genomic testing. The turnaround
time varied, but on average, results were shared with the patient within 6.95 months. Turnaround time was significantly quicker for the 9 patients in the telemedicine group (4.2 months) than for the 35 patients in the in-person group (7.7 months; t=2.159; p< 0.037; Figure 8).

**Figure 8. Genomic test turnaround time by mode.**

The turnaround time for the 44 patients who completed genomic testing with data available varied, but on average, results were shared with the patient within 6.95 months. Turnaround time was significantly quicker for the 9 patients in the telemedicine group (4.2 months) than for the 35 patients in the in-person group (7.7 months; t=2.159; p< 0.037). In these box plots, the boxes extend from the first quartile to the third quartile. Vertical lines go through the boxes at the median. The whiskers go from each quartile to the minimum or maximum.

**VII. Types of referrals placed**

Twenty-seven of the 118 patients evaluated by genetics (25%) received a referral to at least one medical specialist, while 2 others received referrals to allied health professionals.
only. In total, there were 36 medical specialty referrals placed, with ophthalmology being the most common (Figure 9). Specialty clinics were the second most common referral, and included ALS, dementia and memory disorders, Fabry disease, hereditary hemorrhagic telangiectasia, memory and POTS. Audiology, physical therapy and occupational therapy each received 2 referrals. Physical Medicine & Rehabilitation received 3 referrals, including 2 referrals to its neuromuscular subspecialty.

![Figure 9. Types of medical specialist referrals placed.]

The 36 medical specialty referrals placed were categorized. Ophthalmology was the most common, followed by specialty clinics. These included ALS, dementia and memory disorders, Fabry disease, hereditary hemorrhagic telangiectasia, memory and POTS. Cardiology, neurology and physical medicine & rehabilitation generated the next most.

**VIII. Counseling components received: for the individual**

Forty-four of the 118 patients seen by genetics (37%) had contact with the genetics team post visit and/or received answers to their follow-up questions.
Of the patients receiving a molecular or clinical diagnosis (N=26), more than half (14; 54%) were provided new surveillance recommendations. The 19 recommendations were categorized (Table 5).

**Table 5. Surveillance recommendations post diagnosis**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ophthalmologic evaluation</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Other evaluation (swallow study, muscle contracture testing)</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Allied health services (audiology, physical therapy)</td>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td>Specialty clinic (metabolic)</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Further genetic counseling (prenatal)</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Cancer screening</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Lifestyle changes &amp; home treatment</td>
<td>7</td>
<td>37</td>
</tr>
</tbody>
</table>

Ninety percent of patients suspected to have a genetic condition (N=83), including all diagnosed patients (100%) received education on the prognosis of their suspected genetic condition.

Six of the 83 patients (7%) were recommended to receive treatment in the study, including 3 who had received diagnoses. Two of the 6 patients receiving treatments (33%) were managed by genetics. The treatments included an Alzheimer’s medication, an enzyme replacement therapy, two diet interventions, a vitamin and phlebotomy.
Nineteen (73%) were of reproductive age, and 11 (58%) of these received counseling on their reproductive risk.

For 24 of the 26 diagnosed patients (92%), information on the genetic condition was documented and provided to their PCP or referring provider to help guide future clinical management.

Of the 118 patients in the study, 16 (14%) received resources. Resources were defined as things provided to patients that did not have to do with disease management/treatment or education. Resources were provided to 13 patients suspected of having a genetic condition (16%), including 1 patient who did not receive a diagnosis and 100% of those receiving a clinical diagnosis. In total, 21 distinct resources were provided. Types were categorized (Figure 10).
Sixteen out of 118 (14%) patients in the study received resources. The 21 distinct resources were categorized. Mindfulness-based stress reduction was the most common resource provided, followed by websites and clinical trial information. All of the mindfulness-based stress reduction resources were associated with hypermobile Ehlers-Danlos syndrome and hypermobility spectrum disorders.

Of note, 10 total individuals suspected of having a genetic condition, including 1 of the diagnosed individuals, received “other” benefits not matching a pre-planned study variable (Table 6). While these benefits varied based on individual circumstance, 5 patients (50%) were suggested to consider another type of genetic counseling, in particular, cancer counseling (4 patients).
Table 6. Other benefits for the individual

<table>
<thead>
<tr>
<th>Referral recommended for cancer genetic counseling based on family history</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suggested ophthalmology consult which prompted diagnosis of choroideremia, for which he had a known family history</td>
</tr>
<tr>
<td>Discussed seeing a dietician (referral not placed per records)</td>
</tr>
<tr>
<td>Prenatal genetic counseling referral for partner carrier status</td>
</tr>
<tr>
<td>Affirmed her emotional reactions and reinforced the importance of follow-up for counseling to discuss mental health concerns; upon physical exam, confirmed hypermobile EDS, allowing her to obtain PT referral</td>
</tr>
<tr>
<td>Referral to cancer genetic counseling based on fam hx of ovarian cancer</td>
</tr>
<tr>
<td>Referral to cancer genetic counseling for personal hx of melanoma and fam hx of cancer</td>
</tr>
<tr>
<td>Confirmed genetic testing would not make him ineligible for heart transplant</td>
</tr>
<tr>
<td>Blood work identified her as Tay Sachs carrier; provided education on this</td>
</tr>
<tr>
<td>Preconceptional counseling/carrier testing recommended</td>
</tr>
</tbody>
</table>

IX. Counseling components received: for the family

Sixty-two (53%) of the 118 patients evaluated by genetics had a family history of their referred or geneticist suspected condition, while 47 (40%) did not. For 9 (8%) of the patients, family history was not available. Fifty-eight of the 62 (94%) who reported a family history reported one or more first-degree relatives had the referred or geneticist suspected condition.

Testing was ordered for family members of 4 (3%) of the patients evaluated. Three of these family members were alive and received single gene testing, while in one instance the family member was deceased and panel testing was done.
Of the 83 patients suspected to have a genetic condition, 69 (83%; including 100% of the diagnosed patients) received education on the inheritance pattern of the genetic condition. Eighteen patients (22%, including 15 [58%] of the diagnosed patients) received counseling on reproductive risk for their family members. Cascade testing was recommended in 14 diagnosed patients (54%). Three individuals (4%, including 1 in the diagnosed group [1%]) received family counseling.

Six of the diagnosed patients (23%) received a family letter that could be provided to family members explaining the condition, reproductive risks and testing options.

Of patients suspected to have a genetic condition, 6 patients, including 2 patients receiving diagnoses, received “other” benefits for their family during their genetic counseling sessions, detailed in Table 7. Of note, 5 of 6 (83%) were surveillance recommendations/coordination for family members.

**Table 7. Other benefits for the family**

| Recommended that sister seek genetics evaluation based on ophthalmologic issue described |
| Recommended echocardiogram for daughter |
| Discussed sister’s difficulty securing genetic testing and encouraged resources be shared with family |
| Coordination with brother's neurologist at UCI |
| Recommend a renal ultrasound for adult offspring and maternal cousins - arranged by their PCP |
| Testing this patient could find potential explanation for son's features |
X. **Counseling components received: for society**

Of the 118 patients seen by genetics, nearly all (98%) received a clinical note documenting the visit through their PCP or referring provider. To note, the study gathered this information from clinical documentation only; it did not track delivery or receipt of these notes. Therefore, this figure could be low. Two of the patients suspected to have a genetic condition (2%) were referred for research participation following the clinic visit. When the study was designed, the original intention was to collect other components with relevance for society, including whether a particular patient case had been submitted to a journal for publication, whether a case had been discussed at a multi-disciplinary case conference and whether the clinical genetics team had input patient phenotype/genotype data into public databases. However, during the study, it was deemed outside of the scope of the chart review because these data were not available in the electronic medical record.

**DISCUSSION**

This study aimed to explore evidence for utility of genomic medicine approaches in the adult genetics clinic setting. It did so through examining several elements of a genetics evaluation that have previously been extensively studied, such as referral type, number of specialists seen, time from initial symptom presentation to evaluation, diagnostic yield and test follow-through and turnaround time, as well as through characterizing elements that have not been extensively studied, such as education on prognosis, risk assessment, resources and research participation referral. In so doing, it endeavored to document the patient population presenting to genetics, and what genetics is providing to individual patients, their families and society as a whole. It also aimed to determine whether any
statistically significant differences exist in what genetics is providing based on: ancestry; insurance type and whether the evaluation occurred in person (prior to the COVID-19 pandemic) or via telemedicine (during the pandemic).

Prior studies on clinical utility of genomic medicine approaches primarily focused on pediatric audiences or specific disorders. This study aimed to look at adult patients and across indications. Additionally, to the author’s knowledge, there are no similar studies characterizing counseling components received in this population.

The time period of the study provided a unique opportunity to compare genetics evaluations in two appointment modes. Whereas prior to the COVID-19 pandemic the clinic was not offering telemedicine visits as routine practice, the state and local stay-at-home orders that went into place in March 2020 necessitated 44 patient visits (37% of the study data) be conducted via telemedicine. This mode of patient visit is likely to persist in some way even post pandemic, making this type of data useful as a future baseline.

Overall study limitations due to the two-year, retrospective chart review nature include: short timeframe and small sample size; patients first seen at the end of the study collection period may not have been able to complete testing and follow-through, and therefore their testing, diagnostic and counseling component variables may not be accurately coded and captured herein; not representative of true racial/ethnic clinic make-up; limited number of providers working in the clinic may have skewed the data based on personal style and preferences; incomplete information on cases, as details were only pulled from clinical documentation; one clinical geneticist was on leave twice during the study period, which may have influenced the numbers of patients able to be seen; and it was not
possible to include a random sampling of patients not thought to have a genetic condition for adequate comparison, as this was not a prospective study. Other limitations and future directions are described throughout the following sections.

I. Characteristics of patients referred to genetics

In this study, 64% of patients were female. This figure could be explained by the fact that studies have shown that women access health care services at higher rates than men. Additionally, women often drive discussions around reproductive planning, and discussing carrier screening did come up in the study. Ninety-one percent of patients in the study were 18-67, and more than two-thirds (68%) were 18-47. Patients were therefore accessing genetics services during prime reproductive and working years. More patients in the study had private insurance than government insurance (56% versus 44%) and none self-paid.

The race/ethnicity breakdown in the study demonstrated that while the UCI adult genetics clinic had diversity, it did not track with the general population. While the study population was similarly White, it was less Black and Hispanic, and more Asian than the general U.S. population as reported in the 2020 Census (United States Census Bureau, 2021). Additionally, more individuals reported more than one race/ethnicity in pedigrees in this study than in the general population.
Table 8. United States race and Hispanic origin (United States Census Bureau, 2021)

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>White alone</td>
<td>76.3</td>
</tr>
<tr>
<td>White alone, not Hispanic or Latino</td>
<td>60.1</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>18.5</td>
</tr>
<tr>
<td>Black or African American alone</td>
<td>13.4</td>
</tr>
<tr>
<td>Asian alone</td>
<td>5.9</td>
</tr>
<tr>
<td>Two or more races</td>
<td>2.8</td>
</tr>
<tr>
<td>American Indian and Alaska Native alone</td>
<td>1.3</td>
</tr>
<tr>
<td>Native Hawaiian and Other Pacific Islander alone</td>
<td>0.2</td>
</tr>
</tbody>
</table>

These differences are likely due to the fact that census data are collected differently than how data were collected in this study. If race/ethnicity was not already stated in the patient’s electronic medical record, the study author assigned a race/ethnicity based on information provided during the session in the pedigree. Additionally, the local population from which our medical center draws is likely different than the U.S. population overall. However, if this trend were to continue over time, it is interesting to consider that this clinic may offer a somewhat unique opportunity to collect data on Asian populations in particular.

The overwhelming majority of patient visits were driven by referrals from physicians (97%). As this study did not investigate the scheduling pipeline, a limitation is that it is not possible to tell how much of a role, if any, the genetics clinic plays in determining who is
ultimately seen. Because there is a wait list for genetics services at this clinic, there is likely a process by which the clinic team filters patients based on priority, and those factors were not examined here. Regardless, this physician referral figure reinforces the important role that referring providers play in a patient's obtainment of genetics services. Future studies could examine the referring provider specialty to determine any patterns, which may potentially help inform educational or training efforts.

Patients seen at this genetics clinic always saw a genetic counselor and, the majority of the time (80%) saw a clinical geneticist as well. Though we do not have a comparison group without genetic counselor involvement, knowing that the genetic counseling community has called for a more active role in and more evidence on the impact of genetic counseling in precision medicine, these data may provide valuable initial perspective on current clinical interactions between genetic counselors and patients. Future studies could investigate such comparison groups.

Referral reasons varied in this study but the majority (65%) were referred due to suspicion of a genetic diagnosis, followed by family history of a confirmed or suspected genetic condition, for the purpose of discussing previous genetic testing results and more than one reason. The geneticists in this clinic assessed more patients (73%) to have a presentation suspicious for a genetic condition. This is perhaps not surprising given that clinical geneticists receive specialized training in the identification and diagnosis of genetic conditions, including detailed physical examinations looking for dysmorphic and other pathognomonic features, family history collection and knowledge of the characteristics of genetic conditions. While beyond the bounds of this study, it could be interesting to gather data on patient perceptions of the value of these detailed physical examinations, knowing
that 72% received one as part of their evaluation. It could very well be that some satisfaction or anxiety reduction could be observed, as has been shown in the literature on the impact of collecting a detailed family history.

This study collected and categorized testing indications in the adult genetics clinic setting. As Shashi et al. (2014) among others have noted, there is a need for more data on both referral indications and testing indications for adults specifically, as it has been described in published research and anecdotally observed in the field that these would differ from those in the pediatric setting (where things like malformations and developmental delay are common testing indications), but not much evidence has been collected to date. We showed the highest number of testing indications to be for suspected neurodegenerative disorders and connective tissue disorders, followed by skeletal dysplasias, ophthalmologic conditions and metabolic disorders. These indications are perhaps not surprising in this population, as neurodegenerative disorders such as Alzheimer disease and Huntington disease and some types of connective tissue disorders such as hypermobility Ehlers-Danlos syndrome typically present in adulthood.

The mean number of specialists seen prior to genetics in the study was 2.9, quite a bit lower than the literature’s reported 7.3. This could be because medical specialists were measured instead of overall physician consults, and it would be interesting to explore how this figure would change if all physicians including primary care physicians were included. This study revealed a higher mean years from first symptom presentation to genetics evaluation (15.6 years) than the rare disease literature’s reported six-to-eight years to accurate diagnosis. There could be several reasons for this discrepancy, including: the small sample size of the study; this study focusing on genetic etiologies only, versus rare disease
as a whole; this study focuses on adults only; and the center is a university academic medicine setting, which could lend itself to ascertainment bias on this clinic’s patient population being “sicker” or “more complicated” than the average case.

II. What genetics provided: for the individual

This study demonstrated that, following genomic testing, a definitive genetic diagnosis was obtained in 36% of cases. Removing the one patient who was diagnosed with karyotype, it showed a 34% diagnostic yield with NGS testing, a figure in line with or slightly higher than the NGS and exome literature, the majority of which has been conducted in the pediatric setting. While the overall rate is low compared to studies examining “traditional” diagnostic methods in the genetics clinic (which have shown rates of 45-50%; Shashi et al., 2014), it is interesting to see that the NGS yield was replicated even in this small study. A bigger sample size in which one could be certain that testing indications were properly represented would provide more confidence in this figure, as well as in the diagnostic yield by testing indication type data collected herein.

An unexpected finding in the study was that individuals who did not report European ancestry during the pedigree collection were more likely to be diagnosed following genomic testing than those who did: 69% versus 26%, respectively. Given the history of genomics platforms being built with European inputs, it might have been assumed to have found either the opposite, or no difference, based on the small sample size. Findings were constrained by the fact that European ancestry is self-reported during the pedigree collection process. Additionally, one could surmise that this could be a referral bias; in other words, perhaps individuals of European descent may be more likely to self-advocate for a genetics consultation. Finally, it is known from previous studies in the division that individuals who
present for ruling out Ehlers-Danlos syndrome are more likely to be European. Knowing that there were a substantial number of this type of referral, this could be responsible for this figure. Regardless, this finding is certainly worth exploring in this clinic and beyond, to ascertain what factors may be driving it.

The study did not formally capture data on what diagnoses were placed by prior providers, so this information could not be analyzed. However, the study author was aware of several instances where individuals who came to genetics with a previous understanding of a genetic condition diagnosis (in particular, hypermobile Ehlers-Danlos syndrome) were deemed by the clinical team to not have a presentation suspicious for a genetic condition, because they did not meet criteria. In the case of hypermobile Ehlers-Danlos syndrome or hypermobility spectrum disorders, even if patients did meet clinical criteria, there is no molecular testing available. It could be interesting to look more closely at previous diagnoses or provider suspicions in the future, to examine the role of a genetics evaluation in clarifying prior provider suspicions and/or changing prior incorrect diagnoses.

Single-gene disorders were most likely to be molecularly diagnosed in this population with ophthalmologic and neurodegenerative conditions comprising the majority (2 of 2 [100%] and 4 of 8 [50%], respectively). A five-year study conducted by a laboratory previously showed ophthalmology (42%) and dermatology (60%) to have the highest yields with NGS (Hartman et al., 2019). This study’s yield for dermatologic conditions was 33%, a figure based on only 1 patient; this finding would need further validation. It was not surprising to see that 78% of clinical diagnoses made were in connective tissue disorders. The clinical team frequently and increasingly over the past several years has reported receiving referrals for suspected hypermobility type Ehlers-Danlos syndrome as awareness
of this condition has grown among providers and the general public alike. While the scope of this study did not include tracing patient outcomes following genetics evaluation, subsequent testing or other evaluations ordered, or downstream revenue, it could be interesting for institutions to track this information as potential evidence of the value genetics brings to other divisions and allied health services. Additionally, it is important to note that heritable cancer syndromes only represented a small (7%) of diagnoses in this study; this figure is likely misleading. This diagnosis was an incidental finding for a patient originally seen in this clinic for a different indication; the general genetics clinic at UCI does not typically handle cancer referrals. It may be informative to conduct a similar analysis in the cancer genetics clinic; it is likely that the findings may be different in that setting.

Hartman et al. reported a trend showing a decrease in the number of VUSs reported on NGS testing, from 50% in 2012 to 22% in 2017, and it is likely this figure will continue to go down as more and more individuals of diverse backgrounds receive genetic testing (2019). This study showed a VUS rate of 24%, which is in line with these findings. It is important to note that this study represents one point in time only; as new genes are discovered and added to testing, and as VUS are reclassified by laboratories, this rate will undoubtedly change over time, and likely impact the diagnostic rate figures.

Nearly 79% of tests ordered for patients in this study were genomic tests, though biochemical tests, imaging studies and enzyme tests clearly played a role in evaluations, as well. NGS tests contributed to nearly all diagnoses (16 of the 17 diagnoses). For this population, panel tests were far and away the most frequently ordered (53% of the time), and exome sequencing was hardly ever ordered (2 patients; 4% of genomic tests ordered). This is not all that surprising given that ACMG recommends it only in certain cases such as
when single-gene or panel testing is not available or prior testing has been uninformative. As this type of testing inevitably continues to grow in relevance based on its comprehensive and cost effective nature, and as genome sequencing becomes more clinically available, it will be important to examine larger sample sizes of adult populations to glean evidence on clinical utility.

This study showed that significantly more patients seen in-person followed through on their testing than did those seen via telemedicine (77% versus 42%). While we cannot ascertain the reason, we would hypothesize that this has to do with factors inherent to the pandemic. Whereas when patients were seen in person they could frequently get their blood drawn for testing that same day at the medical center, being remote required kits to be shipped to patients’ homes and their shipping them back, or for a subsequent appointment to be scheduled. It is also known that the medical center’s insurance authorization process was slowed during the pandemic; this could have made the number artificially low for telemedicine follow-through. Alternatively, there may have been competing financial or time management stressors for patients during the pandemic.

It was hypothesized that insurance coverage type may have played a role in test follow-through, but these findings suggest it did not. Given that the study also showed post-visit contact between the clinical team and the patients in 37% of cases, this lack of impact could be influenced by the clinical team’s diligent follow-up with insurance authorization processes. While it was not possible to measure time spent on insurance authorization, this is anecdotally known to be a time-consuming part of the clinic staff and provider’s jobs, and would be interesting to explore in a future study.
An interesting and unexpected finding was the quicker test result turnaround time – defined in this study as the time from appointment to results return to the patient – for patients in the telemedicine group (4.2 months versus 7.7 months). While the clinic workflow was not studied, nor was there ability to include any insights from the team, one can surmise that the team’s remote operations enabled some administrative efficiencies for test ordering, or that patients motivated to complete their testing did so very quickly, or that something happened at the laboratory end between 2019 and 2020 that enabled efficiencies with test turnaround. Anecdotally, the team also believes that telemedicine enable some more flexibility at the patient end; for example, they noticed that some patients seen on telemedicine participated from their cars or offices, which would not have happened in an in-person scenario. This flexibility could have explained the quicker follow-up appointments.

It is likely a combination of these factors and would be interesting to compare in-person versus telemedicine in a non-pandemic time. Additionally, this study measured turn-around time as when results were shared with patients. It would be interesting to collect dates from the test reports themselves to truly examine whether the clinic team or laboratory side is driving this timeframe.

Patients in the study received 36 medical specialist and 6 allied health professional/services referrals, with ophthalmology receiving the majority, followed by specialty clinics. This finding is in line with ophthalmologic conditions providing a high number of testing indications/diagnoses. Knowing information about which providers are most likely to be destinations for ongoing surveillance is important for clinics as they consider educational/grand-round efforts within institutions and/or the opportunity to create joint genetics-medical specialty clinics for certain conditions.
A key principle underlying the purpose of genetics evaluations – that of their potential to facilitate early detection and prevention – was illustrated in this study in that more than half of patients (54%) receiving a molecular or clinical diagnosis were provided new surveillance recommendations. Data on patient follow-through on these recommendations were not collected, so it is not possible to measure their impact; an interesting longer term study could be undertaken to examine outcomes following implementation of new surveillance regimens.

The study’s findings that 90% of patients suspected to have a genetic condition and all diagnosed patients received education on their condition is important. Genetics teams spend significant time explaining genes and inheritance patterns. Patient comprehension or interest in this was not gauged, however, which could be worth exploring further through patient surveys.

It is intriguing that only 6 of 83 patients (7%) suspected of having a genetic condition were prescribed a new treatment based on their condition. This figure is likely low because it was not possible to track what other specialists did after the genetic diagnosis, and in many cases, it would be those providers who would manage therapy. It could also be that genetic conditions that onset in adults have fewer treatment options available. Additionally, none of the treatments were gene therapies. The treatments included an Alzheimer's medication, an enzyme replacement therapy, two diet interventions, a vitamin and phlebotomy. This is perhaps not surprising given that gene therapy progress has primarily occurred in conditions that present in childhood and cancer. Knowing that numbers of clinical trials in gene therapies are increasing yearly, it would be interesting to see if this finding persists over the next several years.
Relatively few patients were documented to have received resources in the study (14% overall and 16% of those suspected to have a genetic condition). Resources were defined as things provided to patients that did not have to do with disease management/treatment or education. They are typically part of a genetic counseling results disclosure, so it is possible not all instances were documented, or that the telemedicine format may have limited ability to distribute items like brochures. A larger study would provide better insight into the types of resources most frequently provided and gaps to address.

When examining “other” benefits provided to individuals, discussion of and referral to cancer genetic counseling came up several times. This reinforces the importance of collecting a comprehensive family history in every genetics clinic setting.

III. What genetics provided: for the family

Ninety-four percent of patients reporting a family history in the study had one or more first-degree relatives impacted. It is a common refrain in the community that genetics is “all in the family,” and seeing this born out here validates the practice of including education and risk assessment for family members as part of every genetics results disclosure. Only 58% of the diagnosed patients’ charts reviewed indicated that reproductive risk for family members was specifically discussed, which seems low. It could be that providers opted not to discuss this topic if not relevant for the patient and future pregnancy plans, or perhaps the topic was covered and not documented, and therefore would not have been picked up by the study.
It is clear an individual’s genetics evaluation had broader impact when examining components such as: inheritance pattern education, which occurred 83% of the time for those suspected to have a genetic condition and 100% of the time in diagnosed patients; cascade testing for family members, which was recommended 54% of the time in diagnosed patients; family letter distribution, which occurred 23% of the time in diagnosed patients; and family counseling, which was provided to 4% of individuals suspected to have a genetic condition. The genetics team ordered testing for family members relatively infrequently (3% of patients evaluated); however, as this study did not extend to examining what may have occurred if and when family members followed up on cascade testing recommendations, this figure could be low.

IV. **What genetics provided: for society**

At the outset of the study, it was planned to collect additional variables that could serve as surrogates for value to society, including whether patient cases were shared at genetics division or outside case conferences, if cases were written up for submission to peer-reviewed journals and if patient information was shared in public databases such as GeneMatcher. The scope of the study – a chart review – did not allow for collection of these items, which are not routinely captured in the electronic medical record.

Of interest, a clinical note documenting the visit was sent PCPs/referring providers in nearly all instances (98%), including for those patients not suspected to have a genetic condition. The study did not track delivery/receipt of these notes, so it is possible that this figure is inaccurate. The three patients who did not receive a note per documentation were referred by physicians, so it is possible, and perhaps even likely, that their physicians did in fact receive this information and the available documentation just did not reflect this. While
satisfaction was not measured in this study, it is reasonable to consider that this group of patients, many of whom have spent years and time and money associated with multiple specialist visits, may have found it helpful to spend an hour in genetics sharing their personal and family history and obtaining the advice of an expert who approached things differently than their previous doctors had. The level of patient satisfaction across the board, but in particular for patients who did not receive a diagnosis, could be a good future direction to explore. Additionally, by providing detailed information to patients’ PCPs or referring providers, genetics clinical teams are helping advance the overall medical field’s understanding of genetic conditions.

This study documented a few patients who were referred for research participation following their clinic visit. Assuming these patients followed through, which again, was outside of the scope, this may have helped contribute to the overall genetics community’s goals to better understand and treat rare diseases.

One could argue that all variables collected in the study impact society because healthier people are generally assumed to make for happier, more productive communities. With rare disease economic burden estimated at $1 trillion in the United States in 2019 (EveryLife Foundation, 2021), one could also assume that health efforts aimed at early detection and prevention, such as many of the encounters examined here, would have a positive impact on cost reduction, as well, arguably a good thing for society. An interesting future direction would be a financial modeling study looking at costs incurred by the medical system among those obtaining a diagnosis versus those who do not.
V. Conclusion

This study replicated published clinical utility measures such as diagnostic yield, indicating there is value in genetics evaluations in the adult setting. However, even by replicating diagnostic yield of genomic testing, more than 60% of patients suspected of having a genetic condition were not diagnosed in this study, indicating that there is clearly more work to do from a clinical utility perspective. The study also adds to the evidence pool on what adults are presenting to genetics with, providing information that could potentially help improve the referral stream and reduce time to diagnosis. Importantly, this study showed that genetics is providing more to patients than genomic testing, a final diagnosis and treatment, including offering valuable information, management recommendations and psychosocial support to individuals and families and contributing to societal goals, as well. Clinical geneticists and genetic counselors are trained in early detection, prevention and management, and as such, play a valuable role for their institutions in terms of revenue generation and patient outcomes improvement, and for society through advancing public health imperatives. This study was limited by reviewing charts at a single genetics clinic site with only five clinical geneticists and two genetic counselors, over only two years – and a unique two years at that, given that the study period coincided with the COVID-19 pandemic. Future studies could include a more robust sample and deeper evaluation on subsequent outcomes, revenue generated and patient perceptions of genetics evaluations, and look prospectively at how telemedicine visits differ from the traditional in-person approach. Characterizing the true value of a genetics evaluation is in the best interest of not only patients and the genetics community, but of society at large.
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# APPENDIX

## Appendix A. Variables Collected

### All patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth date</td>
<td>First clinic</td>
</tr>
<tr>
<td>First visit date</td>
<td>Kept first visit?</td>
</tr>
<tr>
<td>Is the note signed?</td>
<td>First visit physician</td>
</tr>
<tr>
<td>First visit genetic counselor</td>
<td>Age at first visit date</td>
</tr>
<tr>
<td>Next visit date</td>
<td>Next visit clinic</td>
</tr>
<tr>
<td>Age at next visit date</td>
<td>Gender</td>
</tr>
<tr>
<td>Zip code</td>
<td>Race/ethnicity (American Indian or Alaska Native; Asian or Pacific Islander; Black; Hispanic; White; More than 1)</td>
</tr>
<tr>
<td>Preferred Language</td>
<td>Insurance Type (HMO, EPO, PPO, Medicare, Medicaid, Tricare, Self Pay)</td>
</tr>
<tr>
<td>Referral indication</td>
<td>Referral type (self or physician)</td>
</tr>
<tr>
<td>Previous genetic testing done (Yes or no)</td>
<td>Previous genetic testing type (Single gene, panel, exome, genome, DTC)</td>
</tr>
<tr>
<td>Previous genetic testing results (Positive, negative, VUS, other)</td>
<td>Previous genetic testing result name</td>
</tr>
<tr>
<td>Given clinical diagnosis of genetic condition previously? (yes or no)</td>
<td>Given molecular diagnosis previously?</td>
</tr>
<tr>
<td>Number of first degree relatives with referred or suspected condition</td>
<td>Type of specialists seen prior to genetics</td>
</tr>
<tr>
<td>(People without genetic diagnosis only): Time from first symptom till first genetics evaluation (Years)</td>
<td>Patient’s main concerns</td>
</tr>
<tr>
<td>Is ancestry provided in pedigree European? (Yes or no)</td>
<td>Ancestry as provided in pedigree</td>
</tr>
<tr>
<td>Ancestry as provided in pedigree</td>
<td>Family history of referred or suspected condition (Yes or no)</td>
</tr>
<tr>
<td>Number of first degree relatives with referred or suspected condition</td>
<td>In person or telemed?</td>
</tr>
<tr>
<td>In person or telemed?</td>
<td>If telemed, video or phone?</td>
</tr>
</tbody>
</table>
(People without molecular Dx only): Genetic diagnosis suspected at first visit?

(People without molecular Dx only): Geneticist suspected diagnosis/differential diagnosis

Was testing ordered for patient? (Yes or no)

What tests ordered for patient (Biochemical, imaging, karyotype, microarray, single gene, panel, exome, genome, pharmacogenomic)

Ordered testing carried out?

Was testing ordered for family member?

Is family member alive or deceased?

What Tests Ordered for Family Member (Biochemical, imaging, karyotype, microarray, single gene, panel, exome, genome, pharmacogenomic)

Ordered testing carried out by family members?

Management guidance to referring provider or PCP sent?

Specialist referral (Yes or no)?

Specialist referral type

Follow-up questions answered or contact

**For patients with a suspected genetic condition only**

Insurance authorization requested for genetic testing?

Insurance authorization obtained for genetic testing?

Genetic test results (Positive, negative, VUS)

Genetic test result name

Genetic test secondary findings?

Time from appointment to genetic test results (Months)

New surveillance recommendations based on molecular diagnosis provided?

New surveillance based on molecular diagnosis recommendations type

Education on prognosis of genetic condition provided?

Treatment provided based on molecular results?

Who manages new treatment (genetics or other specialist)?

Education on inheritance pattern provided?

Reproductive age? (Yes or no)

Reproductive risk assessment for individual provided?

Reproductive risk assessment for family provided?

Cascade testing recommended? (Yes or no)

Family counseling provided? (Yes or no)

Family psychosocial counseling provided? (Yes or no)

Resources provided? (Yes or no)

Resource type

Other benefits as described in plan

Research participation referred?
<table>
<thead>
<tr>
<th><strong>Family letter provided?</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Information on condition documented and sent to PCP or referring provider?</strong></td>
<td></td>
</tr>
</tbody>
</table>