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I, Margret Matias, hereby submit this original work as part of the requirements for the degree of Master of Science in Genetic Counseling.

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Comparison of medical management and genetic counseling options pre- and post-whole exome sequencing for patients with positive and negative results

Student's name: **Margret Matias**

This work and its defense approved by:

Committee chair: Derek Neilson, M.D.

Committee member: Kathleen Collins, M.S.

Committee member: Katherine Healy, M.S.

Committee member: C Alexander Valencia, Ph.D.

Committee member: Xue Zhang, Ph.D.

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**Comparison of medical management and genetic counseling options pre- and post-whole exome
sequencing for patients with positive and negative results**

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Margret A. Matias

B.S. University of Illinois at Urbana-Champaign

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Committee Chair: Derek Neilson, MD

Committee Members: Kathleen Collins, MS, LGC; Katie Wusik, MS, LGC; Xue Zhang, MSPH, PhD;

C. Alexander Valencia, PhD

ABSTRACT

Purpose: Whole exome sequencing (WES) has been found to be a useful clinical diagnostic tool; however, the effect of WES results on patient management has not been extensively studied. The current study investigated changes to medical management and genetic counseling options following WES results as well as the differences in the changes between those with positive and negative results.

Methods: Seventy-eight individuals who had WES at Cincinnati Children's Hospital Medical Center were included in the study. They were separated into two groups: positive results and negative results. Their electronic medical records were retrospectively reviewed to collect data pertaining to medical management and genetic counseling options pre- and post-WES results. The absence (no) or presence (yes) of each outcome was recorded pre- and post-WES results and then analyzed using McNemar's tests to determine if there was a significant pre- to post-WES difference; the positive and negative groups were compared using Fisher's exact tests.

Results: Of the 78 participants included in the study, 37 (47.4%) had positive results and 41 (52.6%) had negative results on WES. The majority (97%) of all participants received one or more changes to medical management and/or genetic counseling options following WES results. Using McNemar's tests, there were statistically significant differences in all categories for those with positive results (genetic testing $p<0.0001$; imaging $p=0.0127$; metabolic testing $p<0.0001$; recurrence risk $p<0.0001$; reproductive options $p<0.0001$; testing for family members $p<0.0001$; support groups $p<0.0001$), and statistically significant differences in three categories for those with negative results (genetic testing $p<0.0001$; imaging $p<0.0001$; and metabolic testing $p<0.0001$). Using Fisher's exact tests to compare the positive and negative groups to each other, participants with positive results showed different types of changes in specialist referrals ($p=0.05$), lifestyle recommendations ($p=0.03$), as well as recurrence risk, reproductive options, testing availability for family members, and support group availability (all $p<0.0001$).

Conclusion: Both the positive and negative groups showed significant changes following WES results in genetic testing, imaging, and metabolic testing. Only the positive group showed significant changes in

specialist referrals, lifestyle recommendations, recurrence risk, reproductive options, testing availability for family members, and support group availability.

Key Words: *clinical impact; genetic counseling; genetic testing; medical management; whole exome sequencing*

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INTRODUCTION

Development of next-generation sequencing technologies has resulted in faster and more cost-efficient genetic testing (Rabbani, Tekin, & Mahdiah, 2014). Whole exome sequencing (WES) uses next-generation sequencing to provide coverage of over 95% of exons. Exons have traditionally been targeted for sequencing because approximately 85% of disease-causing pathogenic variants in humans are hypothesized to be located within exons (Botstein & Risch, 2003; Majewski, Schwartzentruber, Lalonde, Montpetit, & Jabado, 2011; Rabbani, Tekin, & Mahdiah, 2014). The overall diagnostic yield of WES has been shown to range from 21% for proband-only to 37% for trio analysis (Iglesias et al., 2014; Lee et al., 2014; Retterer et al., 2015; Yang et al., 2014), and can exceed 50% when considering specific patient phenotypes such as hearing loss (Farwell et al., 2015; Iglesias et al., 2014; Retterer et al., 2015; Thevenon et al., 2016). In addition to identifying a diagnosis underlying the patient's symptoms, secondary findings may also be identified (Green et al., 2013). The American College of Medical Genetics (ACMG) recommends that laboratories offering WES specifically investigate 56 genes that show evidence of causing severe disease which is preventable if identified before symptoms begin ("ACMG policy statement: updated recommendations regarding analysis and reporting of secondary findings in clinical genome-scale sequencing," 2015). Both primary and secondary findings have been presumed to prompt specific and targeted medical management changes and recommendations for patients and their families, although studies to date have been limited.

Other genetic testing methodologies have been studied in more depth for their impact on management. When chromosomal microarray (CMA) was introduced as a clinical diagnostic tool, its impact on medical management was investigated, and in some studies it has been shown to impact medical management for up to 70% of patients (Coulter et al., 2011; Saam, Gudgeon, Aston, and Brothman, 2008). Examples of changes to medical management in these studies include specialist referrals, ability to provide a revised recurrence risk, changes to medical screening, changes to genetic and/or diagnostic testing, and imaging/lab tests. Riggs et al. (2014) investigated the clinical actionability of CMA results by querying a large genomic database for the rate of positive CMA results that

overlapped at least one region associated with published management recommendations. Of the 4,125 pathogenic/likely pathogenic deletions and duplications in the database, 46% were associated with established clinical management recommendations, which suggests that genetic diagnoses found on CMA can have specific clinical management recommendations that directly impact patients who receive positive results.

Some studies have previously reported that positive WES results prompt changes to medical management recommendations in a majority of patients (Iglesias et al., 2014; Valencia et al., 2015). Valencia et al. (2015) analyzed 40 patients who had undergone WES, 12 of whom had positive results. They found that medical management was altered for 100% of participants with positive WES results in their study. Medical management was defined broadly to include receiving genetic counseling and ending the diagnostic odyssey in addition to changing imaging recommendations and/or medication(s) and initiation of subspecialty consults. Iglesias et al. (2014) also found that of the patients in their study with positive WES results (n=37), 100% received some sort of change to their medical management. All 37 patients who received a diagnosis from WES were able to discontinue further diagnostic investigations, and a subset received additional targeted changes including initiation of screening for other manifestations, changes in their treatment, identifying other family members with gene pathogenic variants, and assisting in reproductive planning.

In addition to altering medical management for patients, receiving a molecular diagnosis has genetic counseling implications and may allow for options that were not previously available, including reproductive options and targeted testing for symptomatic or asymptomatic family members which may prompt changes to their medical management (Dixon-Salazar et al., 2012; Stark et al., 2016). Receiving a specific diagnosis also allows for identification of diagnosis-specific support groups, and families are often able to meet others in a similar situation who can provide empathy, support, and firsthand experiences (Plumridge et al., 2011).

Investigation into how WES results influence medical management and change the availability of genetic counseling options, as well as comparisons between individuals with positive and negative WES

results, are not available. In addition to investigating the impact of WES results on patient management and options as the primary outcome, the current study is differentiated from previous research because outcomes were studied both pre- and post-WES. Evidence describing how WES changes medical management and genetic counseling options could have an impact on the utilization of WES as a clinical diagnostic test, and could also increase access by improving coverage of the test for patients. The purpose of this study was to investigate if medical management and genetic counseling options change following WES results for patients with positive or negative WES results, and to assess whether there are differences between these two groups in regards to the changes seen.

MATERIALS AND METHODS

Participants

This quantitative case-control study was approved by the Cincinnati Children's Hospital Medical Center (CCHMC) Institutional Review Board. The electronic medical records (EMR's) of individuals who underwent whole exome sequencing (WES) were reviewed. Inclusion criteria were: patients whose WES was ordered by a CCHMC provider, whose testing was run and analyzed by the CCHMC Molecular Genetics Laboratory, and whose results were returned between October 1, 2013 and December 31, 2015. Exclusion criteria included receiving a variant of uncertain significance (VUS) in the absence of a positive primary and/or positive secondary finding.

Participant selection process

The CCHMC Molecular Genetics Laboratory's records were used to identify possible participants for the study (Figure 1). Eligible participants (n=102) were sorted into two groups based on their WES results. Those that received negative results with no VUS findings were placed into the negative group (n=54), and those that received positive primary and/or positive secondary results, with or without VUS findings, were placed into the positive group (n=48). All pathogenic or likely pathogenic variants were considered positive results. Individuals in the positive and negative groups were assigned to broad phenotype categories by the research team based on their clinical features, as indicated on the test requisition. These broad phenotypic categories included: immune deficiency, neurologic, dysmorphic

features/multiple congenital anomalies (DF/MCA), hematologic, skeletal, and endocrine. Participants were assigned to one or more broad phenotypic categories. Based on these categorizations, any participants whose assigned category or categories did not have an equivalent match in the opposite group were excluded (n=13). Throughout the data collection process, any individual who did not have a patient record in the EMR system or whose EMR did not contain any pertinent data was excluded (n=8). Participants were further excluded from the study if related to another participant who had the same phenotype, such that only one member of the family was included (n=2), or if a participant's WES results had been reclassified following the initial reporting of results (n=1). There were 37 participants in the positive group and 41 in the negative group included for analysis. All participants included in the final study sample were randomly assigned a unique identification number, and a protected Excel file was created to link each participant to their study ID number.

Medical record review

An online REDCap (Research Electronic Data Capture) database was created to store the data collected for the study. REDCap is a secure, web-based application designed to support data capture for research studies (Harris et al., 2009).

Data on demographics, medical management, and genetic counseling options were collected for each participant. Demographic information included age, sex, race, ethnicity, referring provider and referring provider's specialty, detailed indication for WES, broad phenotype classification, whether testing was proband-only or included additional family members, and the results of WES including any primary, secondary, and/or VUS findings. Additionally, whether or not each participant had a presumed diagnosis in place before they received WES results was recorded.

Following the collection of demographic information for each participant, data on the broad categories of medical management and genetic counseling options were collected both pre and post-WES results. "Medical management" was defined as genetic testing, imaging testing, metabolic testing, specialist referrals, lifestyle recommendations, and recurrence risk. Specific imaging testing collected included skeletal survey, bone age x-ray, brain MRI, echocardiogram, abdominal ultrasound, and renal

ultrasound. Specific metabolic testing collected included urine organic acids, serum amino acids, and acylcarnitine profile. “Genetic counseling options” was defined as reproductive options such as targeted prenatal diagnostic testing and preimplantation genetic diagnosis (PGD), targeted testing availability for family members, and access to diagnosis-specific support groups. All variables were recorded in a binary (yes or no) fashion based upon whether each recommendation was present or available pre- and post-WES results. The full data collection tool is available in Appendix III.

Alternative data collection strategies

There were five participants (6.4%) whose EMR’s did not contain comprehensive data on the desired variables; thus, alternative data collection strategies were utilized. The first alternative method involved consulting published clinical practice guidelines for a patient’s given diagnosis or diagnoses, if available. Published guidelines were available for the diagnoses of three of these five participants. The final alternative method of data collection involved consulting an expert panel of three geneticists within the Division of Human Genetics at CCHMC. These geneticists reviewed the remaining two participants and came to a consensus as to whether medical management changes should be made for each patient based on their WES results and what those medical management changes may be. Recommended changes were recorded in the REDCap database for each respective participant.

During the final stage of data collection, the expert panel was utilized for two other purposes in addition to providing input for the two participants with incomplete data, as outlined above. The first of these was to control for the presence of VUS findings in the positive group. Since individuals with a VUS but otherwise negative results on WES were excluded, the expert panel was consulted to review the data on participants with positive results and a VUS such that only data pertaining to the positive result were recorded. All participants with both positive results and a VUS (n=12) were first reviewed by the primary research team to determine if there was uncertainty regarding whether the data collected were attributable to the primary and/or secondary results rather than to VUS findings. Any participant for whom there was uncertainty (n=4) was reviewed by the expert panel of geneticists. The expert panel reviewed each of these participants’ WES results and the data collected, and any data that was not solely

attributable to the primary and/or secondary finding were excluded. This helped to control for potential bias due to VUS findings being present only in the positive group and not the negative group. The final role of the expert panel was to provide certain additional information for all participants in the study that was not collected during the chart review process, such as whether any of the primary or secondary diagnoses identified by WES would prompt the initiation of a tailored medication or surgery, or would prevent a specific medication or surgery from being recommended.

Statistical analysis

The Statistical Analysis software (SAS) was used for all statistical analyses. Descriptive statistics were summarized using frequency (percentage) for categorical variables, and median (IQR) or mean (SD) for continuous variables depending on the distribution. The primary outcome variables were genetic testing, imaging, metabolic testing, specialist referrals, lifestyle recommendations, recurrence risk, reproductive options, testing available for family members, and support groups. In the positive and negative groups, respectively, the difference in each of the outcome variables pre- to post-WES results was examined using McNemar's tests. To assess the impact of WES results on the changes for each of the outcomes, proportions of individuals that received change(s) were compared between the positive and negative group using Fisher's exact tests. As the change from No to Yes has different clinical meaning compared with the change from Yes to No, to further analyze the pre- to post-WES differences between the positive and negative groups, participants were grouped into four categories: No/No, No/Yes, Yes/No, and Yes/Yes, to separate out the specific types of changes made and the direction of these changes. The proportions of these four categories between the positive and negative groups were compared using Fisher's exact tests. Given the exploratory nature of the study, $p \leq 0.05$ was used for the statistical significance without correcting for multiple testing.

RESULTS

Participant demographics and clinical characteristics

The final study cohort included 78 participants, 37 (47%) of whom had positive WES results and 41 (53%) of whom had negative WES results. The proportions of males and females are comparable, and

the median age was 7 years old (Table 1). The majority (87%) of participants were Caucasian. The most common indication for WES was neurologic phenotype (38%). No statistically significant differences in demographics were found between the positive and negative groups.

Participants had undergone extensive evaluations and testing prior to WES (Table 2), with many having had several types of diagnostic testing and evaluations from multiple specialists. Of the 26 total participants who had a presumed diagnosis before receiving WES results, 13 of those received a positive result and 13 received a negative result. Of the 13 individuals who had a presumed diagnosis and received a positive WES result, WES confirmed the presumed diagnosis in 5 (38%) and altered the diagnosis in 8 (62%).

Medical management

Medical management outcomes pre- to post-WES were first examined among the positive group and the negative group. A significant change from pre- to post-WES was detected for all medical management outcomes analyzed for participants with positive results, while a significant change was detected in genetic testing, imaging, and metabolic testing for participants with negative results (Appendix I). The pre- to post-WES difference could not be statistically analyzed for specialist referrals as this outcome was measured only post-WES.

As the direction of change may have different clinical meanings, the results were summarized into four categories in order to assess the types of changes and compare them between the positive and negative groups: 1) The variable was not recommended pre- or post-WES (No/No), 2) The variable was only recommended post-WES (No/Yes), 3) The variable was only recommended pre-WES (Yes/No), and 4) The variable was recommended both pre- and post-WES (Yes/Yes). As shown in Appendix II, Fisher's exact test detected significant differences between the positive and negative groups in specialist referrals ($p=0.05$), lifestyle recommendations ($p=0.03$), and recurrence risk ($p<0.0001$). More specifically, about twice as many participants in the positive group received specialist referrals following WES (43%) when compared to the negative group (22%), almost five times as many in the positive group received a new lifestyle recommendation post-WES (24%) as compared to those in the negative group

(5%), and almost all participants in the positive group received a new recurrence risk following WES (95%) while almost all of those in the negative group remained without a recurrence risk following WES (98%).

To test whether there was any broad difference between the positive and negative groups, the four categories were collapsed into two groups (Table 3). 1) “No change” indicated the variable was neither recommended before nor after WES results (No/No) or was recommended both before and after WES results (Yes/Yes), indicating there was no difference in the variable before and after WES for that participant. “Change” indicated the variable was either only recommended after WES (No/Yes) or was only recommended before WES (Yes/No), indicating there was a difference in the variable for that participant before and after WES results. Regardless of WES results, the overall proportion of participants with at least one change to medical management was high (97%). Between the positive and negative groups, an overall difference in the proportion of patients with a change was detected in specialist referrals ($p=0.05$) and recurrence risk ($p<0.0001$).

A larger proportion of participants in the positive group received genetic testing, imaging, and metabolic testing post-WES than did participants in the negative group, although the difference was not statistically significant (Figure 2). Post-WES results, 24% in the positive group received genetic testing, compared to 15% in the negative group ($p=0.39$); 57% in the positive group received imaging testing, compared to 37% in the negative group ($p=0.11$); and 11% in the positive group received metabolic testing, compared to 2% in the negative group ($p=0.18$).

Genetic counseling options for patients and families

Genetic counseling options pre- to post-WES were examined among the positive group and the negative group. A significant change from pre- to post-WES was detected in the availability of reproductive options ($p<0.0001$), testing for family members ($p<0.0001$), and support groups ($p<0.0001$) for participants with positive results, while a significant change was not detected in genetic counseling options for participants with negative results (Appendix I).

For each individual outcome, participants were split into the same four categories of 1) No/No, 2) No/Yes, 3) Yes/No, and 4) Yes/Yes, as outlined above. Significant differences between the positive and negative groups were detected for all genetic counseling options outcomes including reproductive options ($p<0.0001$), testing for family members ($p<0.0001$), and support groups ($p<0.0001$), with positive WES results allowing for the availability of these options for the majority of positive patients but negative results not changing the availability of these options for the majority of negative patients (Appendix II). Upon collapsing into two groups of “change” and “no change,” a statistically significant difference between the positive and negative groups remained in all genetic counseling options outcomes. Regardless of WES results, the overall proportion of participants with at least one change to genetic counseling options was 49% (Table 3).

Case illustrations

The following case illustrations allow for an enhanced understanding of the types of targeted changes that patients may receive to medical management and genetic counseling options post-WES results.

Patient 39: Leigh syndrome/ECHS1 deficiency

Patient 39 was three years old at the time WES was ordered and was referred for testing due to movement issues including dystonia, spells of leg weakness, complex stereopathy, and chorea. The patient also presented with high frequency hearing loss and a sacral dimple. WES identified compound heterozygous pathogenic variants in the *ECHS1* gene, which is consistent with a diagnosis of mitochondrial short-chain enoyl-CoA hydratase 1 deficiency, also called “Leigh-like syndrome.” Following the disclosure of these WES results, several changes to medical management were implemented including recommendations for the patient to receive an echocardiogram; referrals to Genetics, Gastroenterology, and Nutrition; and initiation of a diet similar to that used to treat other branch chain amino acidurias with limitations of valine and isoleucine and supplementation with formula. Receiving a genetic diagnosis allowed the family to use this information for reproductive planning

purposes and will allow at-risk family members to pursue targeted testing. Finally, this WES result allowed for the availability of diagnosis-specific support groups for the patient and family.

Patient 49: Activated PI3K-delta immunodeficiency syndrome

Patient 49 was 14 years old at the time WES was ordered and was referred to determine a genetic cause for his clinical diagnosis of combined variable immunodeficiency (CVID). He had initially been referred to CCHMC for workup and evaluation for possible bone marrow transplant (BMT) to treat his immunodeficiency. Several diagnostic studies were performed during his course at CCHMC, including WES, which identified a *de novo* pathogenic variant in the *PIK3CD* gene, consistent with Activated PI3K-delta immunodeficiency syndrome (APDS). Because this was found to be a *de novo* variant, the family could be assured that the recurrence risk to have another child with this condition was low (< 1%), and that testing for other family members was not indicated. Importantly, this diagnosis initiated a targeted treatment plan and also prevented a BMT. Specifically, Sirolimus was started for this patient, which is an mTOR inhibitor that has been shown to improve outcomes in patients with this condition as the mTOR pathway is excessively activated in APDS (Lucas et al., 2014).

Patient 55: Familial Mediterranean fever and Lynch syndrome

Patient 55 was a 13 year old female with a complex medical history including a suspected diagnosis of dyskeratosis congenita with clinical features including recurrent fevers and leukocytosis, leiomyomatosis, hyperhidrosis, plaque-like skin, and esophageal strictures. She was born to consanguineous parents who had two other children with immunodeficiency and other complex medical issues. WES identified both a primary finding and a secondary finding for patient 55. The primary finding identified was homozygous pathogenic variants in the *MEFV* gene, consistent with a diagnosis of Familial Mediterranean Fever (FMF). This primary finding was thought to explain some but not all of her presenting features. Colchicine was initiated for the patient as a targeted treatment for the primary diagnosis of FMF. A secondary finding was also identified: a heterozygous pathogenic variant was found in the *MSH6* gene, which is associated with Lynch syndrome. Because trio testing was performed, it was found that both of the patient's parents harbored the same *MSH6* pathogenic variant; thus, recurrence

risks both for Lynch syndrome as well as constitutional mismatch repair deficiency (CMMRD), which occurs when biallelic pathogenic variants in *MSH6* are inherited, were able to be provided to the family. In addition to this, it was recommended that the patient and affected family members be referred to a clinic that specializes in hereditary cancer predisposition. In this case, both of the diagnoses made on WES had important implications for the patient's medical management as well as for family members.

DISCUSSION

The purpose of this study was to assess the effect of WES results on medical management and genetic counseling options for patients receiving positive or negative WES results and to determine if there are differences between the positive and negative results groups.

Overall, 100% of participants with positive results and 95% of participants with negative results were found to have at least one change in their medical management and/or genetic counseling options pre- to post-WES results. The proportion of participants in the positive group that experienced changes is higher than what studies on chromosomal microarray (CMA) have reported (Coulter et al., 2011; Henderson et al., 2014; Saam et al., 2008), which report that up to 70% of patients with positive CMA results received changes to management. However, these studies measured changes differently than the current study because they looked only at management following testing results. The pre- to post-test measurement method that was utilized in the current study may have been able to detect changes that would be missed by a medical record review or survey that only considers documentation after the testing of interest has been done. This pre- to post-test method collects a broader scope of information and may be considered a less targeted but more comprehensive way to look at patient management. This may contribute to why the rate of change identified in the current study is higher than what has been previously reported in CMA studies.

Statistically significant changes following WES results were identified for participants with positive results in all medical management and genetic counseling categories. Thus, positive WES results may be informative to many aspects of a patient's care and the options available to them. Some of these changes can be predicted based on the implications of having a genetic diagnosis, such as being able to

perform targeted testing for a future pregnancy or targeted testing in an at-risk family member. Patients with positive results may experience changes to any one of the medical management and genetic counseling categories, and specific proportions of patients who may receive changes to a specific management category can be predicted based on the data presented in this study. Additionally, despite some patients being given a presumed or clinical diagnosis before WES, most patients with a presumed diagnosis who received positive WES results received an altered diagnosis upon receiving their result; therefore, they may need to be managed differently based on this new accurate diagnosis.

For individuals with negative results, statistically significant differences were identified following WES results in the following categories: genetic testing, imaging, and metabolic testing. All of these changes were discontinuation of recommendations in these categories following WES results. Negative WES results, therefore, may help guide subsequent management, specifically by preventing unnecessary additional genetic testing, imaging, and metabolic studies. Negative results may also be informative to families because anticipatory guidance about what kinds of changes they may expect to see following WES can be provided.

Depending on an individual's symptoms, genetic testing, imaging, and metabolic testing are commonly performed during the workup for an individual with a suspected but undiagnosed genetic disorder. These tests may also be important tools for screening and management of individuals who have a genetic diagnosis. The different ways that these tests are utilized may contribute to why significant differences pre- and post-WES were identified for participants with both positive and negative WES results. The fact that participants in both groups experienced changes in genetic testing, imaging, and metabolic testing may explain why no significant differences were found between the two groups in these categories. Both positive and negative WES results can influence the initiation, continuation, or termination of certain testing. In some instances a positive diagnosis must be confirmed or further studied via follow up genetic testing methodologies. An example of this is seen with patient 23, for whom WES identified homozygous pathogenic variants in the *NPR2* gene, causative of Acromesomelic Dysplasia, Maroteaux type. Trio testing identified that the variant was paternally inherited, with the father being

unaffected as he was heterozygous for this variant. A SNP microarray was performed subsequently and confirmed paternal uniparental disomy. Another example is seen with patient 9, for whom WES identified a heterozygous *XIAP* pathogenic variant consistent with X-linked lymphoproliferative syndrome type 2. This condition would seem to explain her presenting features but typically females with the condition have two pathogenic variants; no heterozygous females have ever been reported. Following WES, targeted deletion/duplication testing of *XIAP* was ordered and was negative. Next, X-inactivation testing was ordered which showed a skewed X-inactivation pattern in the patient with a ratio of 96:4. To determine if there was an abnormality such as a gross deletion or X-autosome translocation affecting the typical X chromosome copy which could explain the uneven X-inactivation pattern, chromosome analysis and microarray were ordered for this patient and were normal. Finally, *XIST* gene sequencing was ordered as a last attempt to provide an explanation for the X-inactivation pattern in the patient. This testing again came back negative. Thus, the skewed X-inactivation likely explains the patient's diagnosis.

More commonly, however, both positive and negative WES results prevented further genetic testing (76% and 85% of patients in the positive and negative groups, respectively). Positive WES results most often prevented the need for further genetic testing due to identifying a genetic cause for the patient's presenting features, while negative WES results frequently prevent further genetic testing as well because there may be no further testing that can be offered.

Like the trend seen in genetic testing, changes pre- to post-WES in imaging and metabolic testing were similar between the positive and negative groups. For participants with negative WES results, 56% received no additional imaging studies following WES results. Of participants with positive WES results, 46% experienced a change in their imaging recommendations. A majority (82%) of these terminated additional imaging following WES results, and 18% initiated new imaging. Participants with negative results experienced more discontinuation of imaging than did those with positive results, while participants with positive results experienced more initiation of imaging than did those with negative results. This difference in imaging recommendations was not statistically significant between participants with positive and negative WES results. Both positive and negative results may be informative in

preventing further imaging studies for patients, while positive results can also be informative by prompting new imaging studies that would not have been recommended had a molecular diagnosis not been identified on WES. Both positive and negative results can help to tailor testing decisions for patients.

Changes to metabolic testing were seen in 43% of those in the positive group and in 46% of those in the negative group. In both groups, all participants with changes experienced discontinuation of metabolic testing. Because participants both with positive and negative WES results had similar differences in pre- to post-WES imaging and metabolic testing, there was no significant difference between the positive and negative groups. WES results, no matter if they are positive or negative, seem to influence testing decisions made following WES. This may be because both positive and negative WES results are informative to the clinician. Besides the obvious implications of a positive result being informative by providing a genetic diagnosis, a negative result may also be informative because it can rule out a number of suspected diagnoses that were on the differential diagnosis list prior to WES being performed. This may allow the clinician to be reassured that testing or screening that had been recommended due to a suspected diagnosis may be discontinued or changed based on this new information from the negative WES result.

Another interesting finding is that there was a greater rate of additional genetic testing, imaging, and metabolic testing post-WES results for those in the positive group compared to those in the negative group, regardless of whether or not these tests had been done pre-WES. Although the difference was not statistically significant likely due to small sample sizes, it may be that receiving a molecular diagnosis on WES allows for additional testing that is more targeted than would be done for someone without a diagnosis.

Though not analyzed in a pre- to post-WES fashion, the rate of post-WES specialist referrals was compared between the positive and negative groups. A marginally significant difference was detected when comparing the positive group to the negative group ($p=0.05$), with almost twice as many individuals in the positive group receiving specialist referrals (43%) compared to the negative group (22%). Positive

results may help the patient's healthcare providers to better understand the underlying etiology for their condition and be aware of additional symptoms or health concerns that may need to be monitored regularly, which can spur additional screening regimens and referrals to specialists who can appropriately manage them.

While participants in both the positive and negative groups had significant differences following WES in genetic testing, imaging, and metabolic testing, only those with positive results had differences in the other medical management categories. Positive results initiated new lifestyle recommendations (dietary recommendations, physical activity recommendations, targeted pharmacologic treatments, and/or avoidance of a medication/procedure/surgery) for all positive participants that received a change in this category. For patient 39, a dietary restriction was implemented as the primary treatment for the genetic diagnosis identified on WES. The recommended diet restricted valine and isoleucine, as the ECHS1 enzyme is involved in the breakdown of these amino acids and when not functioning properly leads to the buildup of these compounds. While it is possible for undiagnosed patients to receive lifestyle recommendations based on their symptoms, they are often not tailored to the underlying cause of the patient's features. Because negative results did not show significant changes to lifestyle recommendations, there was a significant difference between the positive and negative groups in this category.

Similarly, the medical management category of recurrence risk showed significant differences only for patients with positive results. Receiving a molecular diagnosis can impact a patient and his or her family by allowing the family to be given an exact recurrence risk, which allows parents and other relatives to make informed decisions about their reproductive choices and future pregnancies (Henderson et al., 2014). In some cases, more than one recurrence risk can be given. For example, in the case of patient 55, risk numbers could be given both for recurrence of Lynch syndrome as well as occurrence of CMMRD based on the identification of a pathogenic variant in *MSH6*. A recurrence risk could also be given for the primary diagnosis, meaning the family was provided with three new recurrence risks following WES. Particularly when trio WES is performed, a diagnosis provides a recurrence risk not only

to the proband but also to the biological parents of the proband. Several studies have shown that recurrence risk as well as the parents' perception of this risk plays a large role in their reproductive decision-making (Bailey et al., 2003; Selkirk et al., 2009), as does the potential to use technology such as PGD or prenatal exclusion testing, which requires a genetic diagnosis (Decruyenaere et al., 2007; Downing 2005; Klitzman et al., 2007).

The most significant difference in the effects of positive versus negative WES results is seen when looking at genetic counseling options including reproductive options, testing availability for family members, and support group availability. Without a genetic diagnosis, families with a child who has a presumed genetic condition that has not been confirmed molecularly do not have the option to pursue targeted prenatal testing or preimplantation genetic testing. The availability of support groups is also something that affects not only the proband but also parents, family members, and others close to the proband. They allow for identification of others with the same diagnosis and reduced feelings of isolation, provide help in navigating health and social care as relevant to the diagnosis, and provide other forms of support and connection that are supplementary to the support provided by health and social care professionals (Plumridge et al., 2011). The majority of individuals with negative WES results remained without available diagnosis-specific support groups post-WES results, while diagnosis-specific support groups became available to the majority of those that received positive results on WES. The effect of WES results can extend beyond treatment and medical decisions and can also extend beyond the proband. It is important to consider how additional individuals such as family members may be impacted from receiving a diagnosis on WES.

Limitations and future directions

This study was conducted at a single pediatric institution and the majority of the participants were Caucasian; therefore, it is unknown whether or not the findings are generalizable to other patient populations. Studies utilizing larger sample sizes will provide more power to detect significant associations if they exist. Only specific types of medical management were investigated during this

study. For example, limited information about medications was collected. Future studies could investigate medication changes due to WES results in more depth.

There is an inherent limitation in the medical record review design in that there is variability from one patient's chart to the next. For this reason, alternative data collection strategies were utilized for some participants, which may lead to a potential source of bias. In addition, reviewer bias is possible because the data collectors were not blinded to the participants' WES results.

It is not possible to determine with the current study if a patient's WES result was the sole reason for the changes identified. It is important to explore other possible explanations for the changes that were observed in the patient population. For example, negative imaging studies or metabolic studies may be reassuring to the clinician and prevent additional testing regardless of if the patient received WES testing. Additional studies that compare the study outcomes between individuals who have not received WES and those that have should be considered. This would help discern whether WES itself is impacting the changes seen or if there are other factors which are responsible for or contribute to these changes. Finally, additional investigation into how VUS results impact changes to patient recommendations would be helpful to understand how all results, not just positive and negative, may alter a patient's course.

Conclusion

This is the first study to look specifically at how medical management and genetic counseling options are impacted by both positive and negative WES results and whether there are differences between these groups. There were statistically significant differences pre- to post-WES in genetic testing, imaging, metabolic testing, lifestyle recommendations, recurrence risk, reproductive options, testing availability for family members, and support groups for participants in the positive group. There were statistically significant differences pre- to post-WES in genetic testing, imaging, and metabolic testing for participants with negative WES results. The vast majority of participants in both the positive and negative groups who experienced changes in these categories had discontinuation of these tests following WES. Overall the changes in recommendations for genetic testing, imaging, and metabolic testing were similar between participants with positive and negative WES results. This helps to illustrate the possible

clinical utility of WES, regardless of the results, in guiding testing decisions and additional workup after WES. Even though no significant difference exists between the positive and negative groups in genetic testing, imaging, and metabolic testing, there was a trend of higher rates of follow-up testing after WES in all three of these testing categories for participants with positive results. There were twice as many specialist referrals for those with positive results compared to those with negative results. These findings provide evidence of the clinical utility of WES, regardless of whether a diagnosis is identified.

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TABLES AND FIGURES

Table 1: Patient demographics and clinical characteristics

	Positive WES results (n=37)	Negative WES results (n=41)	p	Overall (n=78)
Sex			1.00	
Female	20 (54%)	23 (56%)		43 (55%)
Male	17 (46%)	18 (44%)		35 (45%)
Age (years)	8.1 (3.4-14.3)	6.3 (2.8-14.3)	0.76	7.0 (2.8-14.3)
Race			0.18	
Caucasian	30 (81%)	37 (93%)		67 (87%)
Other	7 (19%)	3 (8%)		10 (13%)
Phenotype classification			0.98	
Immune	10 (27%)	9 (22%)		19 (24%)
Neurologic	13 (35%)	17 (41%)		30 (38%)
MCA/DF	1 (3%)	3 (7%)		4 (5%)
Hematologic	1 (3%)	1 (2%)		2 (3%)
Skeletal	1 (3%)	0 (0%)		1 (1%)
Endocrine	1 (3%)	1 (2%)		2 (3%)
Immune + Hematologic	1 (3%)	1 (2%)		2 (3%)
Neurologic + MCA/DF	7 (19%)	8 (20%)		15 (19%)
Immune + MCA/DF	2 (5%)	1 (2%)		3 (4%)
Number of samples analyzed			0.07	
Singleton	3 (8%)	0 (0%)		3 (4%)
Doubleton	2 (5%)	1 (3%)		3 (4%)
Trio	25 (68%)	36 (90%)		61 (79%)
More than trio	7 (19%)	3 (8%)		10 (13%)
¹ De novo	12 (32%)	--	--	--
¹ Inheritance			--	
AD	22 (55%)	--		--
AR	11 (27.5%)	--		--
XL	4 (10%)	--		--
Other	3 (7.5%)	--		--
² Secondary findings	--	--	--	8 (10%)
³ VUS			--	
Yes	12 (32%)	--		--
No	25 (68%)	--		--

Note: age was shown as median (IQR), and compared between patients with positive and negative WES results using Wilcoxon rank sum test; other variables were shown as frequencies (%) and compared using Fisher's exact test.

¹ De novo rate and inheritance pattern were calculated for all positive diagnoses, with some individual participants having more than one positive diagnosis.

² Secondary findings were calculated by the percentage of all participants with a secondary finding, with or without a primary finding.

³ VUS findings shown only for patients with positive WES results since patients with VUS findings in the absence of positive WES results were excluded.

Table 2: Pre-WES characteristics and testing workup of all study participants

	Positive WES results	Negative WES results	Overall
Had presumed dx	13 (35%)	13 (32%)	26 (33%)
Genetic testing	36 (97%)	39 (95%)	75 (96%)
¹ Total # of genetic tests performed	5.1 ± 3.6	4.1 ± 2.1	4.6 ± 2.9
Imaging studies	32 (86%)	38 (93%)	70 (90%)
¹ Total # of imaging tests performed	5.9 ± 6.2	4.7 ± 4.3	5.3 ± 5.3
Metabolic testing	20 (54%)	20 (49%)	40 (51%)
¹ Total # of metabolic tests performed	2.6 ± 1.8	2.6 ± 2.1	2.6 ± 2.0
¹Total # of specialists seen	9.4 ± 3.6	8.9 ± 4.1	9.1 ± 3.9

Note: Variables shown as frequencies (%).

¹ Total numbers are shown as mean ± SD.

Table 3: Comparison of pre- to post-WES changes to medical management and genetic counseling options between positive and negative WES results

	Positive WES results	Negative WES results	p	Overall
Medical Management	37 (100%)	39 (95%)	0.49	76 (97%)
Genetic testing	27 (73%)	33 (80%)	0.59	60 (77%)
Imaging	17 (46%)	23 (56%)	0.50	40 (51%)
Metabolic testing	16 (43%)	19 (46%)	0.82	35 (45%)
Specialist referrals	16 (43%)	9 (22%)	0.05*	25 (32%)
Lifestyle recommendations	9 (24%)	5 (12%)	¹ 0.24	14 (18%)
Recurrence risk	35 (95%)	0	<0.0001*	35 (45%)
Genetic Counseling Options	36 (97%)	2 (5%)	<0.0001*	38 (49%)
Reproductive options	36 (97%)	0	<0.0001*	36 (46%)
Testing available for family members	36 (97%)	0	<0.0001*	36 (46%)
Support groups available	23 (62%)	2 (5%)	<0.0001*	25 (32%)
Any Clinical Impact	37 (100%)	39 (95%)	0.49	76 (97%)

Note: Variables shown as frequencies (%) and compared using Fisher's exact test. The frequencies and percentages shown in the table represent the proportion of participants in the positive and negative groups that received a change to that outcome pre- to post-WES. This analysis was performed after collapsing the four groups of No/No, Yes/Yes, No/Yes, and Yes/No into two groups of "change" or "no change." Significant findings are highlighted with an asterisk (*).

¹ Lifestyle recommendations was not significant using the analysis shown; however, this outcome became statistically significant when participants were broken down further into four groups (No/No, Yes/Yes, No/Yes, and Yes/No) (see Appendix II).

Figure 1: Participant selection process

Figure 2: Frequency of follow-up testing post-WES

Note: Numbers are shown as percentages and compared using Fisher's exact test.

Appendix I: Pre- to post-WES differences in the positive and negative groups

Genetic testing (GT)							
		Post-WES					
		Positive WES results			Negative WES results		
		No GT done post-WES	GT done post-WES	p	No GT done post-WES	GT done post-WES	p
Pre-WES	No GT done pre-WES	1	0	<.0001	2	0	<.0001
	GT done pre-WES	27	9		33	6	

Note: Data shown are frequencies. p values are from exact McNemar tests.

Imaging testing (IT)							
		Post-WES					
		Positive WES results			Negative WES results		
		No IT done post-WES	IT done post-WES	p	No IT done post-WES	IT done post-WES	p
Pre-WES	No IT done pre-WES	2	3	0.0127	3	0	<.0001
	IT done pre-WES	14	18		23	15	

Metabolic testing (MT)							
		Post-WES					
		Positive WES results			Negative WES results		
		No MT done post-WES	MT done post-WES	p	No MT done post-WES	MT done post-WES	p
Pre-WES	No MT done pre-WES	17	0	<.0001	21	0	<.0001
	MT done pre-WES	16	4		19	1	

Lifestyle recommendations (LR)							
		Post-WES					
		Positive WES results			Negative WES results		
		No LR given post-WES	LR given post-WES	p	No LR given post-WES	LR given post-WES	p
Pre-WES	No LR given pre-WES	23	9	0.0039	30	2	1.0000
	LR given pre-WES	0	5		3	6	

Recurrence risk (RR)							
		Post-WES					
		Positive WES results			Negative WES results		
		No RR given post-WES	RR given post-WES	p	No RR given post-WES	RR given post-WES	p
Pre-WES	No RR given pre-WES	1	35	<.0001	40	0	--
	RR given pre-WES	0	1		0	1	

[illegible]

		Post-WES					
		Positive WES results			Negative WES results		
		No RO available post-WES	RO available post-WES	p	No RO available post-WES	RO available post-WES	p
Pre-WES	No RO available pre-WES	0	36	<.0001	41	0	--
	RO available pre-WES	0	1		0	0	

Testing for family members (TFM)	
1	1
2	2
3	3
4	4
5	5
6	6
7	7
8	8
9	9
10	10
11	11
12	12
13	13
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95	95
96	96
97	97
98	98
99	99
100	100

		Post-WES					
		Positive WES results			Negative WES results		
		No TFM available post- WES	TFM available post-WES	p	No TFM available post- WES	TFM available post-WES	p
Pre-WES	No TFM available pre- WES	0	36	<.0001	41	0	--
	TFM available pre- WES	0	1		0	0	

Support groups (SG)

		Post-WES					
		Positive WES results			Negative WES results		
		No SG available post-WES	SG available post-WES	p	No SG available post-WES	SG available post-WES	p
Pre-WES	No SG available pre-WES	6	23	<.0001	29	1	1.0000
	SG available pre-WES	0	8		1	10	

Appendix II: Comparison of pre- to post-WES changes to medical management and genetic counseling options between positive and negative WES results

	¹ Pre	Post	Positive WES results	Negative WES results	p	
Medical Management	Genetic testing	No	No	1 (3%)	2 (5%)	0.54
		Yes	Yes	9 (24%)	6 (15%)	
		No	Yes	0	0	
		Yes	No	27 (73%)	33 (80%)	
	Imaging	No	No	2 (5%)	3 (7%)	0.15
		Yes	Yes	18 (49%)	15 (37%)	
		No	Yes	3 (8%)	0	
		Yes	No	14 (38%)	23 (56%)	
	Metabolic testing	No	No	17 (46%)	21 (51%)	0.37
		Yes	Yes	4 (11%)	1 (2%)	
		No	Yes	0	0	
		Yes	No	16 (43%)	19 (46%)	
	Specialist referrals	No	No	21 (57%)	32 (78%)	0.05*
		Yes	Yes	0	0	
		No	Yes	16 (43%)	9 (22%)	
		Yes	No	0	0	
	Lifestyle recommendations	No	No	23 (62%)	30 (73%)	0.03*
		Yes	Yes	5 (14%)	6 (15%)	
		No	Yes	9 (24%)	2 (5%)	
		Yes	No	0	3 (7%)	
	Recurrence risk	No	No	1 (3%)	40 (98%)	<0.0001*
		Yes	Yes	1 (3%)	1 (2%)	
		No	Yes	35 (95%)	0	
		Yes	No	0	0	
Genetic Counseling Options	Reproductive options	No	No	0	41 (100%)	<0.0001*
		Yes	Yes	1 (3%)	0	
		No	Yes	36 (97%)	0	
		Yes	No	0	0	
	Testing for family members	No	No	0	41 (100%)	<0.0001*
		Yes	Yes	1 (3%)	0	
		No	Yes	36 (97%)	0	
		Yes	No	0	0	
	Support groups	No	No	6 (16%)	29 (71%)	<0.0001*
		Yes	Yes	8 (22%)	10 (24%)	
		No	Yes	23 (62%)	1 (2%)	
		Yes	No	0	1 (2%)	
	Note: Variables shown as frequencies (%) and compared using Fisher's exact test. All four groups (No/No, Yes/Yes, No/Yes, and Yes/No) were included in the Fisher's exact tests. Significant findings are highlighted with an asterisk (*). ¹ Changes to each outcome pre- to post-WES were broken down into four groups. 1) No/No means the recommendation/option was not in place pre- or post-WES; 2) Yes/Yes means the recommendation/option was in place both pre- and post-WES; 3) No/Yes means the recommendation/option was not in place pre-WES but was in place post-WES; 4) Yes/No means the recommendation/option was in place pre-WES but was not in place post-WES.					

Appendix III: Data collection form (see next page)

Demographics

Unique Record ID	<hr/>
Date today (of data collection)	<hr/>
Date of birth	<hr/>
Date WES was ordered	<hr/>
Date WES results were reported	<hr/>
	(Check chart notes first, then use results review)
Age	<hr/>
	(Age when WES was ordered, in months)
Sex	☐ Male ☐ Female
Race	☐ American Indian/Alaska Native ☐ Asian ☐ Black/African-American ☐ Native Hawaiian/Other Pacific Islander ☐ White/Caucasian ☐ Other ☐ Not listed
Ethnicity	☐ Hispanic ☐ Non-Hispanic ☐ Not listed
Referring provider name	<hr/>
Referring provider specialty	<hr/>
Indication/phenotype for WES	<hr/>
Broad indication/phenotype	☐ Immune deficiency ☐ Neurologic ☐ MCA/dysmorphic features ☐ Hematologic ☐ Skeletal ☐ Endocrine
Singleton, doubleton, or trio?	☐ Singleton ☐ Doubleton ☐ Trio ☐ More than trio ☐ Not listed
Positive primary findings?	☐ Yes ☐ No
Inheritance pattern	☐ AD ☐ AR ☐ XL ☐ Mitochondrial ☐ Other
If other, list:	<hr/>

Zygosity

- ☐ Heterozygous
☐ Homozygous
☐ Hemizygous
☐ Compound heterozygous
☐ Other

If other, list:

Gene

Mutation

If compound heterozygous, second mutation

Condition

Segregation

- ☐ Maternal
☐ Paternal
☐ De novo
☐ Not listed

Full or partial diagnosis?

- ☐ Full
☐ Partial
☐ Not listed

Second positive primary findings?

- ☐ Yes
☐ No

Inheritance pattern

- ☐ AD
☐ AR
☐ XL
☐ Mitochondrial
☐ Other

If other, list:

Zygosity

- ☐ Heterozygous
☐ Homozygous
☐ Hemizygous
☐ Compound heterozygous
☐ Other

If other, list:

Gene

Mutation

If compound heterozygous, second mutation

Condition

Segregation

- ☐ Maternal
☐ Paternal
☐ De novo
☐ Not listed

Full or partial diagnosis?

- ☐ Full
☐ Partial
☐ Not listed

Positive secondary findings?

- ☐ Yes
☐ No
☐ Opted out

Inheritance pattern

- ☐ AD
☐ AR
☐ XL
☐ Mitochondrial
☐ Other

If other, list:

Zygosity

- ☐ Heterozygous
☐ Homozygous
☐ Hemizygous
☐ Compound heterozygous
☐ Other

If other, list:

Gene

Mutation

If compound heterozygous, second mutation

Condition

Segregation

- ☐ Maternal
☐ Paternal
☐ De novo
☐ Not listed

VUS?

- ☐ Yes
☐ No

Inheritance pattern

- ☐ AD
☐ AR
☐ XL
☐ Mitochondrial
☐ Other

If other, list:

Zygosity

- ☐ Heterozygous
☐ Homozygous
☐ Hemizygous
☐ Compound heterozygous
☐ Other

If other, list:

Gene

Mutation

If compound heterozygous, second mutation

Condition

Segregation

- ☐ Maternal
☐ Paternal
☐ De novo
☐ Not listed

Second VUS?

- ☐ Yes
☐ No

Inheritance pattern

- ☐ AD
- ☐ AR
- ☐ XL
- ☐ Mitochondrial
- ☐ Other

If other, list:

Zygosity

- ☐ Heterozygous
- ☐ Homozygous
- ☐ Hemizygous
- ☐ Compound heterozygous
- ☐ Other

If other, list:

Gene

Mutation

If compound heterozygous, second mutation

Condition

Segregation

- ☐ Maternal
- ☐ Paternal
- ☐ De novo
- ☐ Not listed

BEFORE: Diagnostic Testing

Genetic testing ordered?

- ☐ Yes
☐ No

If yes, check all that apply:

- ☐ Karyotype/FISH
☐ Microarray
☐ Single gene testing
☐ Panel gene testing
☐ Mitochondrial genome analysis
☐ Other

If other, list:

Date of most recent genetic tests (Y-M-D):

All previous genetic testing negative?

- ☐ Yes
☐ No

If genetic testing not negative, results of most recent:

Total number of karyotype/FISH:

Total number of microarray:

Total number of single gene testing:

Total number of panel gene testing:

Total number of mitochondrial genome testing:

Total number of other genetic testing:

Source (date of note, provider initials):

Imaging testing ordered:

- ☐ Yes
☐ No

If yes, check all that apply:

- ☐ Chest x-ray
- ☐ Abdominal x-ray
- ☐ Spine x-ray
- ☐ Bone age x-ray
- ☐ Skeletal survey
- ☐ Other x-ray
- ☐ Whole body MRI
- ☐ Brain MRI
- ☐ Spine MRI
- ☐ Other MRI
- ☐ Abdominal ultrasound
- ☐ Renal ultrasound
- ☐ Echocardiogram
- ☐ Other ultrasound
- ☐ Head CT
- ☐ Chest CT
- ☐ Whole body CT
- ☐ Other CT
- ☐ Other imaging testing

If other imaging, list:

Date of most recent imaging tests (Y-M-D):

Results of most recent imaging tests:

Total number of chest x-ray:

Total number of abdominal x-ray:

Total number of spine x-ray:

Total number of bone age x-ray:

Total number of skeletal survey:

Total number of other x-ray:

Total number of whole body MRI:

Total number of brain MRI:

Total number of spine MRI:

Total number of other MRI:

Total number of abdominal ultrasound:

Total number of renal ultrasound:

Total number of echocardiogram:

Total number of other ultrasound:

Total number of head CT:

Total number of chest CT:

Total number of whole body CT:	<hr/>
Total number of other CT:	<hr/>
Total number of other imaging testing:	<hr/>
Source (date of note, provider initials):	<hr/>
Other testing ordered:	☐ Yes ☐ No
If yes, check all that apply:	☐ Serum amino acids ☐ Acylcarnitine ☐ Carnitine ☐ Lactate ☐ Pyruvate ☐ Urine organic acids ☐ Thyroid (T4/TSH) ☐ Electrography (ECG, EEG, EMG, etc.) ☐ Other
If other, list:	<hr/>
Date of most recent other testing (Y-M-D):	<hr/>
Results of most recent other testing:	<hr/>
Total number of serum amino acids:	<hr/>
Total number of acylcarnitine:	<hr/>
Total number of carnitine:	<hr/>
Total number of lactate:	<hr/>
Total number of pyruvate:	<hr/>
Total number of urine organic acids:	<hr/>
Total number of thyroid (T4/TSH):	<hr/>
Total number of electropgraphy (ECG, EEG, EMG, etc.):	<hr/>
Total number of other other testing:	<hr/>
Source (date of note, provider initials):	<hr/>

AFTER: Diagnostic Testing

Genetic testing ordered?

- ☐ Yes
☐ No

If yes, check all that apply:

- ☐ Karyotype/FISH
☐ Microarray
☐ Single gene testing
☐ Panel gene testing
☐ Mitochondrial genome analysis
☐ Other

If other, list:

Date of most recent genetic tests (Y-M-D):

All genetic testing negative?

- ☐ Yes
☐ No

If genetic testing not negative, results of most recent:

Total number of karyotype/FISH:

Total number of microarray:

Total number of single gene testing:

Total number of panel gene testing:

Total number of mitochondrial genome testing:

Total number of other genetic testing:

Source:

- ☐ Patient chart
☐ Published guidelines
☐ Referring provider
☐ Expert panel

List source:

Imaging testing ordered:

- ☐ Yes
☐ No

If yes, check all that apply:

- ☐ Chest x-ray
- ☐ Abdominal x-ray
- ☐ Spine x-ray
- ☐ Bone age x-ray
- ☐ Skeletal survey
- ☐ Other x-ray
- ☐ Whole body MRI
- ☐ Brain MRI
- ☐ Spine MRI
- ☐ Other MRI
- ☐ Abdominal ultrasound
- ☐ Renal ultrasound
- ☐ Echocardiogram
- ☐ Other ultrasound
- ☐ Head CT
- ☐ Chest CT
- ☐ Whole body CT
- ☐ Other CT
- ☐ Other imaging testing

If other imaging, list:

Date of most recent imaging tests (Y-M-D):

Results of most recent imaging tests:

Total number of chest x-ray:

Total number of abdominal x-ray:

Total number of spine x-ray:

Total number of bone age x-ray:

Total number of skeletal survey:

Total number of other x-ray:

Total number of whole body MRI:

Total number of brain MRI:

Total number of spine MRI:

Total number of other MRI:

Total number of abdominal ultrasound:

Total number of renal ultrasound:

Total number of echocardiogram:

Total number of other ultrasound:

Total number of head CT:

Total number of chest CT:

Total number of whole body CT: _____

Total number of other CT: _____

Total number of other imaging testing: _____

Source: ☐ Patient chart
☐ Published guidelines
☐ Referring provider
☐ Expert panel

List source: _____

Other testing ordered: ☐ Yes
☐ No

If yes, check all that apply: ☐ Serum amino acids
☐ Acylcarnitine
☐ Carnitine
☐ Lactate
☐ Pyruvate
☐ Urine organic acids
☐ Thyroid (T4/TSH)
☐ Electrography (ECG, EEG, EMG, etc.)
☐ Other

If other, list: _____

Date of most recent other testing (Y-M-D): _____

Results of most recent other testing: _____

Total number of serum amino acids: _____

Total acylcarnitine: _____

Total carnitine: _____

Total lactate: _____

Total pyruvate: _____

Total urine organic acids: _____

Total thyroid (T4/TSH): _____

Total electrography (ECG, EEG, EMG, etc.): _____

Total other other testing: _____

Source: ☐ Patient chart
☐ Published guidelines
☐ Referring provider
☐ Expert panel

List source:

BEFORE: Recommendations

Working diagnosis?

- ☐ Yes
☐ No

If yes, list:

Source (date of note, provider initials):

Specialties that have evaluated the patient:

- ☐ Genomic Evaluation Clinic
☐ Genetics
☐ Audiology
☐ Cardiology
☐ DDBP
☐ Endocrinology
☐ ENT
☐ GI
☐ Hematology
☐ Immunology
☐ Nephrology
☐ Neurology
☐ Oncology
☐ Ophthalmology
☐ Orthopedics
☐ Psychiatry/psychology
☐ Pulmonology
☐ Urology
☐ PT
☐ OT
☐ ST
☐ Other

If other specialty, list:

Total number of specialties that have evaluated the patient:

Source (date of note, provider initials):

Lifestyle recommendations:

- ☐ Yes
☐ No

If yes, check all that apply:

- ☐ Diet
☐ Exercise/Physical Activity
☐ Drug/Alcohol Usage
☐ Stress level
☐ Other

If other, list:

Source (date of note, provider initials):

Recurrence risk estimate:

- ☐ Yes
☐ No

If yes, select:

- ☐ Low/close to 0% (presumed de novo)
- ☐ 25%
- ☐ 50%
- ☐ Other

If other, list:

Source (date of note, provider initials):

AFTER: Recommendations

Referral to new specialties?

- ☐ Yes
☐ No

If yes, select all that apply:

- ☐ Genomic Evaluation Clinic
☐ Genetics
☐ Audiology
☐ Cardiology
☐ DDBP
☐ Endocrinology
☐ ENT
☐ GI
☐ Hematology
☐ Immunology
☐ Nephrology
☐ Neurology
☐ Oncology
☐ Ophthalmology
☐ Orthopedics
☐ Psychiatry/psychology
☐ Pulmonology
☐ Urology
☐ PT
☐ OT
☐ ST
☐ Other

If other specialty, list:

Total number of referrals to new specialties:

Source:

- ☐ Patient chart
☐ Published guidelines
☐ Referring provider
☐ Expert panel

List source:

Stop following any specialties?

- ☐ Yes
☐ No

If yes, select all that apply:

- ☐ Genomic Evaluation Clinic
- ☐ Genetics
- ☐ Audiology
- ☐ Cardiology
- ☐ DDBP
- ☐ Endocrinology
- ☐ ENT
- ☐ GI
- ☐ Hematology
- ☐ Immunology
- ☐ Nephrology
- ☐ Neurology
- ☐ Oncology
- ☐ Ophthalmology
- ☐ Orthopedics
- ☐ Psychiatry/psychology
- ☐ Pulmonology
- ☐ Urology
- ☐ PT
- ☐ OT
- ☐ ST
- ☐ Other

If other specialty, list:

Total number of stopped specialties:

Source:

- ☐ Patient chart
- ☐ Published guidelines
- ☐ Referring provider
- ☐ Expert panel

List source:

Lifestyle recommendations discussed:

- ☐ Yes
- ☐ No

If yes, check all that apply:

- ☐ Diet
- ☐ Exercise/Physical Activity
- ☐ Drug/Alcohol Usage
- ☐ Stress level
- ☐ Other

If other, list:

Source (date of note, provider initials):

Lifestyle recommendations:

- ☐ Yes
- ☐ No

If yes, check all that apply:

- ☐ Diet
- ☐ Exercise/Physical Activity
- ☐ Drug/Alcohol Usage
- ☐ Stress level
- ☐ Other

If other, list:

Source:

- ☐ Patient chart
- ☐ Published guidelines
- ☐ Referring provider
- ☐ Expert panel

List source:

Recurrence risk discussed:

- ☐ Yes
- ☐ No

If yes, select:

- ☐ Low/close to 0% (presumed de novo)
- ☐ 25%
- ☐ 50%
- ☐ Other

If other, list:

Source (date of note, provider initials):

Recurrence risk estimate:

- ☐ Yes
- ☐ No

If yes, select:

- ☐ Low/close to 0% (presumed de novo)
- ☐ 25%
- ☐ 50%
- ☐ Other

If other, list:

Source (date of note, provider initials):

- ☐ Patient chart
- ☐ Published guidelines
- ☐ Referring provider
- ☐ Expert panel
- ☐ Inferred

List source:

BEFORE: Available Options

Reproductive options available?

- ☐ Yes
☐ No

If yes, check all that apply:

- ☐ PGD
☐ Prenatal diagnostic testing

Total number reproductive options:

Source (date of note, provider initials):

Genetic testing available for family members?

- ☐ Yes
☐ No

Source (date of note, provider initials):

Access to support groups?

- ☐ Yes
☐ No

Source (date of note, provider initials):

AFTER: Available Options

Reproductive options discussed?

- ☐ Yes
☐ No

If yes, select all that apply:

- ☐ PGD
☐ Prenatal diagnostic testing

Source (date of note, provider initials):

Reproductive options available?

- ☐ Yes
☐ No

If yes, check all that apply:

- ☐ PGD
☐ Prenatal diagnostic testing

Total number reproductive options:

Source:

- ☐ Patient chart
☐ Published guidelines
☐ Referring provider
☐ Expert panel
☐ Inferred

List source:

Genetic testing for family members discussed?

- ☐ Yes
☐ No

Source (date of note, provider initials):

Genetic testing available for family members?

- ☐ Yes
☐ No
☐ Not needed (de novo)

Source:

- ☐ Patient chart
☐ Published guidelines
☐ Referring provider
☐ Expert panel
☐ Inferred

List source:

Access to support groups discussed?

- ☐ Yes
☐ No

Source (date of note, provider initials):

Access to support groups?

- ☐ Yes
☐ No

Source(s):

- ☐ Patient chart
- ☐ Published guidelines
- ☐ Referring provider
- ☐ Expert panel
- ☐ Inferred

List source:

2AFTER: Diagnostic Testing

Second positive finding?

- ☐ Yes
☐ No

Genetic testing ordered?

- ☐ Yes
☐ No

If yes, check all that apply:

- ☐ Karyotype/FISH
☐ Microarray
☐ Single gene testing
☐ Panel gene testing
☐ Mitochondrial genome analysis
☐ Other

If other, list:

Date of most recent genetic tests (Y-M-D):

All genetic testing negative?

- ☐ Yes
☐ No

If genetic testing not negative, results of most recent:

Total number of karyotype/FISH:

Total number of microarray:

Total number of single gene testing:

Total number of panel gene testing:

Total number of mitochondrial genome testing:

Total number of other genetic testing:

Source:

- ☐ Patient chart
☐ Published guidelines
☐ Referring provider
☐ Expert panel

List source:

Imaging testing ordered:

- ☐ Yes
☐ No

If yes, check all that apply:

- ☐ Chest x-ray
- ☐ Abdominal x-ray
- ☐ Spine x-ray
- ☐ Bone age x-ray
- ☐ Skeletal survey
- ☐ Other x-ray
- ☐ Whole body MRI
- ☐ Brain MRI
- ☐ Spine MRI
- ☐ Other MRI
- ☐ Abdominal ultrasound
- ☐ Renal ultrasound
- ☐ Echocardiogram
- ☐ Other ultrasound
- ☐ Head CT
- ☐ Chest CT
- ☐ Whole body CT
- ☐ Other CT
- ☐ Other imaging testing

If other imaging, list:

Date of most recent imaging tests (Y-M-D):

Results of most recent imaging tests:

Total number of chest x-ray:

Total number of abdominal x-ray:

Total number of spine x-ray:

Total number of bone age x-ray:

Total number of skeletal survey:

Total number of other x-ray:

Total number of whole body MRI:

Total number of brain MRI:

Total number of spine MRI:

Total number of other MRI:

Total number of abdominal ultrasound:

Total number of renal ultrasound:

Total number of echocardiogram:

Total number of other ultrasound:

Total number of head CT:

Total number of chest CT:

Total number of whole body CT: _____

Total number of other CT: _____

Total number of other imaging testing: _____

Source: ☐ Patient chart
☐ Published guidelines
☐ Referring provider
☐ Expert panel

List source: _____

Other testing ordered: ☐ Yes
☐ No

If yes, check all that apply: ☐ Serum amino acids
☐ Acylcarnitine
☐ Carnitine
☐ Lactate
☐ Pyruvate
☐ Urine organic acids
☐ Thyroid (T4/TSH)
☐ Electrography (ECG, EEG, EMG, etc.)
☐ Other

If other, list: _____

Date of most recent other testing (Y-M-D): _____

Results of most recent other testing: _____

Total number of serum amino acids: _____

Total number of acylcarnitine: _____

Total number of carnitine: _____

Total number of lactate: _____

Total number of pyruvate: _____

Total number of urine organic acids: _____

Total number of thyroid (T4/TSH): _____

Total number of electrography (ECG, EEG, EMG, etc.) _____

Total number of other other testing: _____

Source: ☐ Patient chart
☐ Published guidelines
☐ Referring provider
☐ Expert panel

List source:

2AFTER: Recommendations

Second positive findings?

- ☐ Yes
☐ No

Referral to new specialties?

- ☐ Yes
☐ No

If yes, select all that apply:

- ☐ Genomic Evaluation Clinic
☐ Genetics
☐ Audiology
☐ Cardiology
☐ DDBP
☐ Endocrinology
☐ ENT
☐ GI
☐ Hematology
☐ Immunology
☐ Nephrology
☐ Neurology
☐ Oncology
☐ Ophthalmology
☐ Orthopedics
☐ Psychiatry/psychology
☐ Pulmonology
☐ Urology
☐ PT
☐ OT
☐ ST
☐ Other

If other specialty, list:

Total number of referrals to new specialties:

Source:

- ☐ Patient chart
☐ Published guidelines
☐ Referring provider
☐ Expert panel

List source:

Stop following any specialties?

- ☐ Yes
☐ No

If yes, select all that apply:

- ☐ Genomic Evaluation Clinic
- ☐ Genetics
- ☐ Audiology
- ☐ Cardiology
- ☐ DDBP
- ☐ Endocrinology
- ☐ ENT
- ☐ GI
- ☐ Hematology
- ☐ Immunology
- ☐ Nephrology
- ☐ Neurology
- ☐ Oncology
- ☐ Ophthalmology
- ☐ Orthopedics
- ☐ Psychiatry/psychology
- ☐ Pulmonology
- ☐ Urology
- ☐ PT
- ☐ OT
- ☐ ST
- ☐ Other

If other specialty, list:

Total number of stopped specialties:

Source:

- ☐ Patient chart
- ☐ Published guidelines
- ☐ Referring provider
- ☐ Expert panel

List source:

Lifestyle recommendations discussed:

- ☐ Yes
- ☐ No

If yes, check all that apply:

- ☐ Diet
- ☐ Exercise/Physical Activity
- ☐ Drug/Alcohol Usage
- ☐ Stress level
- ☐ Other

If other, list:

Source (date of note, provider initials):

Lifestyle recommendations:

- ☐ Yes
- ☐ No

If yes, check all that apply:

- ☐ Diet
- ☐ Exercise/Physical Activity
- ☐ Drug/Alcohol Usage
- ☐ Stress level
- ☐ Other

If other, list:

Source:

- ☐ Patient chart
- ☐ Published guidelines
- ☐ Referring provider
- ☐ Expert panel

List source:

Recurrence risk discussed:

- ☐ Yes
- ☐ No

If yes, select:

- ☐ Low/close to 0% (presumed de novo)
- ☐ 25%
- ☐ 50%
- ☐ Other

If other, list:

Source (date of note, provider initials):

Recurrence risk estimate:

- ☐ Yes
- ☐ No

If yes, select:

- ☐ Low/close to 0% (presumed de novo)
- ☐ 25%
- ☐ 50%
- ☐ Other

If other, list:

Source (date of note, provider initials):

- ☐ Patient chart
- ☐ Published guidelines
- ☐ Referring provider
- ☐ Expert panel
- ☐ Inferred

List source:

2AFTER: Available Options

Second positive finding?

- ☐ Yes
☐ No

Reproductive options discussed?

- ☐ Yes
☐ No

If yes, select all that apply:

- ☐ PGD
☐ Prenatal diagnostic testing

Source (date of note, provider initials):

Reproductive options available?

- ☐ Yes
☐ No

If yes, check all that apply:

- ☐ PGD
☐ Prenatal diagnostic testing

Total number reproductive options:

Source:

- ☐ Patient chart
☐ Published guidelines
☐ Referring provider
☐ Expert panel
☐ Inferred

List source:

Genetic testing for family members discussed?

- ☐ Yes
☐ No

Source (date of note, provider initials):

Genetic testing available for family members?

- ☐ Yes
☐ No
☐ Not needed (de novo)

Source:

- ☐ Patient chart
☐ Published guidelines
☐ Referring provider
☐ Expert panel
☐ Inferred

List source:

Access to support groups discussed?

- ☐ Yes
☐ No

Source (date of note, provider initials):

Access to support groups?

- ☐ Yes
☐ No

Source(s):

- ☐ Patient chart
- ☐ Published guidelines
- ☐ Referring provider
- ☐ Expert panel
- ☐ Inferred

List source: