Exome Sequencing Reanalysis: Past practices and patient characteristics at a single institution

Lauren Rosier
Indiana University
Benjamin M. Helm
Indiana University
Francesco Vetrini
Indiana University
Kayla M. Treat
Indiana University
Amy M. Breman
Indiana University
Erin Conboy (econboy@iu.edu)
Indiana University

Research Article

Keywords: Exome Sequencing, Reanalysis, Clinical Guidelines, Genetic Counseling

Posted Date: May 17th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1653267/v1

Abstract

We performed a cross-sectional, retrospective review of our institution's previous uninformative exome sequencing (ES) results and reanalysis process, and we identified areas of improvement in our genetic testing pipeline. To accomplish this, we performed a detailed chart review of patients who had ES performed from 2013 through 2016 and catalogued data including age, indication for testing, ordering physician specialty, and if a reanalysis was performed. Our final sample included 165 patients with uninformative exome sequencing results, 50 of whom also had reanalysis. Then, descriptive statistics and Fishers exact tests were performed to identify factors associated with whether ES reanalysis had been completed or not. We found that certain factors were more closely associated with a patient having had a reanalysis performed for a normal or uninformative result, like whether the patient had a future appointment within our institution ($p = 0.0276$). Other factors more closely associated with a patient having reanalysis were if the patient met with a geneticist ($p = 0.0018$) and/or genetic counselor ($p = 0.0027$). Other variable such as age, race, and if the patient had a future appointment with their ordering provider were not associated with an increased likelihood of having reanalysis. These results highlight the value of genetics professionals in interpreting complex genetic testing and also identify areas where we may need to improve our current processes. In addition, our results confirm findings from previous studies, implement a basis for other clinics to examine their ES reanalyses pipeline, and allow us to support the call for additional guidelines on ES reanalysis.

Introduction

As the genetics field advances both in technology and our understanding of the genetic basis of disease, we have seen rapid changes in clinical practices and guidelines. Most recently, the American College of Medical Genetics and Genomics (ACMG) recommended that exome sequencing (ES) should be considered as the first or second-tier diagnostic test for those with congenital anomalies or intellectual/developmental delay (ID/DD) diagnosed under the age of 18 years (Manickam et al., 2021). Clinical use of ES has increased over the past decade, and the average molecular diagnostic rate ranges between 25.2–36.7% (Meng et al., 2017; Moreno-De-Luca et al., 2021; Yang et al., 2014). This indicates that approximately 65–75% of those who undergo ES do not receive a diagnosis. For these patients, reanalysis of their ES results provides the opportunity to identify a diagnosis years after the original testing is performed.

While there is currently no official definition of reanalysis, for the purpose of this study, reanalysis is defined as re-examining a patient’s initial ES data using new molecular or clinical information, as well as the most recent literature. A recent paper by Robertson et al (2022) provided a proposed definition of reanalysis to be “an umbrella term that describes the review of existing clinical genomic data from an individual and re-evaluation as a term to describe the review of a variant.” Reanalysis can sometimes reveal a molecular diagnosis previously unidentified or justify the reclassification of a variant of uncertain significance (VUS) to a pathogenic or likely pathogenic variant. Pathogenic variants not previously reported in ES can be a result of improved bioinformatics, novel candidate genes confirmed to be

associated with genetic disease, evolving patient phenotype, and improved genetic knowledge (Wenger, Guturu, Bernstein, & Bejerano, 2017). Past studies examining the clinical utility of ES reanalysis show an increased diagnostic rate of approximately 15% (Baker et al., 2019; Ewans et al., 2018). One study found that in diagnostic reanalyses, 64–75% were due to newly identified disease genes and 6–14% were due to upgraded variant classifications (i.e., VUS to pathogenic) (Liu et al., 2019). Despite the possibility of increased diagnostic success when utilizing reanalysis, there are no published studies examining the clinical uptake of reanalysis as a tool in evaluating patients or the factors that may influence a clinician's decision to initiate reanalysis.

Reanalysis has historically been initiated by clinicians directly contacting laboratories with requests to reanalyze the original data for their undiagnosed patients. For the laboratory, this was typically a manual process (Liu et al., 2019). Given the rate at which new genes are associated with disease and our evolving understanding of pathogenic mechanisms, the need for more structured reanalysis practices and automation has increased. In addition, genome sequencing (GS) has become increasingly more popular as costs have continued to decrease, this may lead some to question the decision to order a reanalysis over GS. When ES and GS are compared clinically, 86% of those with negative ES also had negative GS and 5% had inconclusive GS results (Alfares et al., 2018). This suggests a diagnostic yield of 9% for GS after ES compared to the 11–15% diagnostic yield of ES reanalysis. This direct comparison highlights the potential impact of ES reanalysis. Other studies have examined the cost-effectiveness of reanalysis compared to traditional genetic testing pathways (Stark et al., 2019). This all provides information on the various perspectives of ES reanalysis but does not provide direct guidance for when clinician should be initiating ES.

There are clearly benefits to reanalyzing ES data, but the rapid evolution of genetic knowledge and testing strategies have created challenges for clinics and providers to establish the best practices for ES reanalysis. This is particularly difficult given the lack of consensus in the literature on when a reanalysis of ES should be initiated. Some studies suggest that clinicians should be ordering reanalysis every 12 months to allow for the greatest likelihood of finding an answer for these patient (Ewans et al., 2018). However, there is little descriptive data on when reanalysis is being ordered and for which patients or clinical indications. We sought to address this gap with a retrospective, cross-sectional study aimed at evaluating the ES and reanalysis practices at our institution for a specified time period. The goal was to identify associations between patients who had ES performed with and without reanalysis. This information allows us to recognize opportunities to improve patient care and identify patients who are strong candidates for a reanalysis of their ES.

As clinicians and genetics providers adapt to the recent ACMG guidelines for ES, we expect the number of patients eligible for reanalysis will increase. Our study aims to examine aspects of the process by which reanalysis is pursued at our institution. Additionally, any patient commonalities in those who underwent reanalysis will help us identify or prioritize certain groups of patients for ES reanalysis. By gathering this information, not only will it help genetics providers ensure we are providing the best patient care possible, but this may also allow for identification of opportunities to allow us to further educate providers who

may be ordering ES. This will afford us the chance to examine the clinical uptake of reanalysis at our institution, patient commonalities in those who underwent reanalysis, and identify areas in which we may improve patient care in our institution.

Methods

We utilized a retrospective, descriptive study design involving a cross-sectional analysis of data for a pre-specified time period. The protocol for this study required review from the Indiana University Institutional Review Board (Protocol: #11120) and this study was deemed exempt status and approved. Inclusion criteria for this study were patients seen at Riley Hospital for Children at Indiana University Health who had non-diagnostic ES results using our program's preferred commercial laboratory between January 2013 and December 2016. While there are several genetic testing laboratories utilized by our institution, we chose to narrow the patient sample to the laboratory most utilized by the genetics department at our institution. The time frame of 2013–2016 encompasses the oldest ES orders from the laboratory and allowed for ample time for providers to have ordered reanalysis. We collaborated with the laboratory to obtain a list of every patient at our institution who had undergone ES at our institution. We then built a database in REDCap and populated it with relevant information including test name, ordering physician specialty, and test result (positive, negative, or VUS). Study data were collected and managed using REDCap electronic data capture tools hosted by Indiana University (Harris et al., 2009; Harris et al., 2019). In addition to ES results, basic demographic and clinical information were collected for each patient. Demographic information included age, race, insurance, provider, and vital status. Clinical information included last appointment, future appointments, family history, if patient was seen by a geneticist or genetic counselor, and dates of ES and reanalysis. A full list of variables collected can be found in the supplemental materials.

Individual chart reviews were performed using Cerner the electronic medical record system (EMR). Data collection was performed by a single person to avoid discrepancies and was reviewed by a clinical geneticist. Outcomes of interest were (1) to determine if reanalysis had been ordered and (2) to identify patient commonalities in those who did have reanalysis ordered. Descriptive statistics and statistical analyses were carried out on all data and included percentages, mean, median, and standard deviation for applicable variables as appropriate. To identify unadjusted associations between categorical variables, we used Fisher's exact tests and reported two-sided p-values. In exploratory analyses, we tested for possible association between age of the patients and probability of ES reanalysis using simple logistic regression; when appropriate we report the associated Wald χ^2 two-sided p-values. We used $\alpha = 0.05$ for 95% confidence for statistical inference and hypothesis-testing. Statistical analyses were performed using SAS version 9.4 (SAS institute, Cary, NC).

Results

Initially, there were 176 patients that met our inclusion criteria. However, eleven patients were incorrectly included based on the completed test type and were removed from the data set. Our final data set

consisted of 165 patients. Their characteristics and demographic data are summarized in Table 1. A full report of our data and our collection instrument can be found in the supplemental materials. For our patients, 58/165 (35%) received a negative result for their original ES report and 107/165 (65%) received a VUS.

Table 1
Table describing the demographical information of our patient sample

Characteristic	Number of patients (%)
Vital status	
Living	156 (*94.5*)
Deceased	9 (*5.5*)
Insurance Type	
Private	110 (*67.1*)
Public (Medicaid/Medicare)	54 (*32.9*)
Race/Ethnicity	
White	153 (*93.3*)
Black/African American	7 (*4.3*)
Asian	2 (*1.2*)
Hispanic	2 (*1.2*)
Patient Age at time of ES	
Average	9.2 years
Range	1 week – 54 years
Original ES Result	
Negative	58 *(35.2)*
VUS	107 *(64.8)*
Reanalysis Performed	
Yes	50 *(30.3)*
No	115 *(69.7)*
Reanalysis Results	
Negative	25 *(50%)*
VUS	18 *(36%)*
Pathogenic	7 *(14%)*
Average Time from ES to Reanalysis	3.21 years *(1.12 standard deviation)*

Appointment Information

Future appointment information, either at our institution or with their ordering provider, was reviewed up to the most recent encounter date. Of the 165 patients, 80 (48%) had a future appointment scheduled indicating that nearly half had longitudinal follow-up and established care at our institutional. We found that 136 (82.9%) of patients were given specific information to follow-up with their ordering provider; however, only 30 (18%) had a future appointment with the provider who originally ordered their ES. These results suggest that 85 (51%) patients were no longer being seen by our providers, and 134 (81%) patients were no longer following with their original ES-ordering clinician. Notably, 148 (89%) of our patients had been evaluated by a geneticist, and 134 (81%) of our patients had met with a genetic counselor.

Original ES Data

We investigated the influence that an ordering provider's specialty may have on whether a reanalysis is performed and found that the majority of ES were ordered by geneticists (85%). The only other specialties who ordered ES were neurology (2.4%) and oncology/hematology (12.7%). It is worth noting that one of the geneticists is board-certified in pediatric neurology and medical genetics and was categorized as a geneticist in this study. Twenty-three (14%) of our patients had proband-only sequencing, two (1%) of our patients had duo sequencing, and 139 (84%) of our patients had trio testing performed. Figure 1 summarizes the indications that the physicians cited for ordering ES, classified based on the most affected organ systems with a simplified set of choices based on previous literature (Klee et al., 2021). We also provided an "other" category for patients with uncommon indication reasons such as family history of related issues, hematological, and gastrointestinal features. Notably, this is not an exhaustive list.

Descriptive Caption for Accessibility: This is a graph depicting the indications that the patients in this study received exome sequencing for. Approximately 130 patients had a neurological indication, 20 had a musculoskeletal indication, 10 with multiple congenital anomalies, 30 with a congenital anomaly, 10 with immunological indications, about 15 with metabolic indications, and approximately 55 with indications "other" than those specified.

Clinical Documentation

In 27 (16%) patients, the electronic medical record (EMR) did not contain a copy of their original ES laboratory report. In some cases, where the original laboratory report was unavailable, we were able to find the reanalysis laboratory report scanned into the EMR. Where the reanalysis report was available, but the original report was not, the reanalysis reports did not provide information on the original result, only what the reanalysis reported. Further, we had only two cases (1.2%) in which a physician or genetic counselor documented the potential for reanalysis in their clinical pre-test summaries. In both of those cases, the provider did not specify when reanalysis might be available. For those who had a reanalysis performed, 49 (98%) had the laboratory report available in their medical record.

Reanalysis Results

Of the 165 patients in our study, 50 (30.3%) had a reanalysis performed, and the mean time between a patient's ES and subsequent reanalysis was 3.19 years (SD = 1.12 years). In 20% (10/50) of these cases, there was a change to the original indication for testing. This suggests that a patient may have had new clinical symptoms arise or other affected family members identified. This information is useful as it may help identify patients with a higher diagnostic yield on a reanalysis. In a small number of cases reanalysis was either not performed or performed but not resulted despite being pursued by physicians or patients themselves. Results are summarized in Table 1 and Fig. 2.

Figure 2 Description of ES results for patients who underwent reanalysis and the resulting reanalysis outcomes

Descriptive Caption for Accessibility: Flowchart denoting how exome sequencing results changed from the original test to their reanalysis. 50 patients recevied a reanalysis with 15 having a negative result and 35 with a variant of uncertain significance (VUS). Of the 15 negative results, after reanalysis, 7 were still negative, 6 recevied a VUS, and 2 tests returned pathogenic results. Of the 35 original VUS results, 18 were negative after reanalysis, 12 were a VUS after reanalysis, and 5 were pathogenic.

Factors influencing likelihood of reanalysis

We then sought to identify factors associated with whether reanalysis was completed or not. Table 2 summarizes the statistically significant variables of interest.

Table 2
Statistically significant proportions and results between variables of interest and if reanalysis was completed

Variable	Proportion of those with Reanalysis	Fisher's Exact p-value
Insurance		**0.0109**
Private	40/110 (36%)	
Medicare/Medicaid	9/54 (17%)	
Future appointment at IUH		**0.0276**
Yes	31/80 (39%)	
No	19/85 (22%)	
Evaluated by a Geneticist		**0.0018**
Yes	50/148 (34%)	
No	0/17 (0%)	
Met with a Genetic Counselor		**0.0278**
Yes	46/134 (34%)	
No	4/30 (13%)	
Provided Follow-Up Info		**0.0442**
Yes	46/136 (34%)	
No	4/28 (14%)	

First, every patient who had reanalysis had also met with a geneticist, and it was more likely for a patient who had reanalysis to have also met with a genetic counselor ($p = 0.0027$). Second, there was no statistically significant difference between the original ES result type (i.e., negative vs. variant of uncertain significance) and the likelihood of the patient having undergone reanalysis ($p = 0.3817$). This reveals that providers are not showing a bias for ordering reanalysis for patients with a particular result, e.g., only when variants of uncertain significance are identified. It was also more common for patients with private insurance to have had reanalysis performed ($p = 0.0109$). In addition, patients with a future appointment at our institution were more likely to have had reanalysis ($p = 0.0276$), but an appointment with the ordering provider was not significant ($p = 0.2722$). Last, patients who were given specific follow-up information from their providers were more likely to have had reanalysis performed ($p = 0.0442$).

Other statistical analyses performed but found not to be statistically significant with a patient undergoing reanalysis included vital status, age, ethnicity, and family history. Our patient age range was very wide, including neonates at 3 days of age to adults at 54 years of age. While age was not statistically

significant, it is worth noting that 60% of our patients who had reanalysis performed were older children (4-12.99 years).

Discussion

Our study provides a unique insight into our institutional practices surrounding comprehensive genetic testing and highlights a need to examine our current ES and reanalysis processes in the rapidly evolving genetics landscape. The most impactful results of our study are the emphasized importance of a genetics provider being involved in a patient's care, lack of follow-up with genetics providers, underutilization of reanalysis for ES performed during a specific time period, and that patients with private insurance were more likely to have had reanalysis performed. This provides a chance to reflect upon possible causes of these associations and improve our systems to allow for more effective patient care.

Earlier studies have examined patient views of the use of exome sequencing in a variety of settings, cost-effectiveness of reanalysis, and other items (Baker et al., 2019; Meng et al., 2017; Robertson et al., 2022; Wenger et al., 2017). We are not aware of other studies that have examined the ES reanalysis practices at a single institution. By performing reviews such as this, we can ensure our system is as efficient as possible and improve patient care for all disciplines. When discussing the reanalysis results themselves, 14% (7/50) of our patients who underwent reanalysis received an updated positive or pathogenic result. This is in line with the reported yield of reanalysis by other studies (Baker et al., 2019; Ewans et al., 2018). In addition, 35% (18/50) received a variant of uncertain significance. These results emphasize the rapid expansion of knowledge and evolving clinical phenotypes. In situations where genetic results are uncertain, providers can use clinical judgement to provide a clinical diagnosis. In addition, 14% of reanalyses resulting in pathogenic variants emphasizes the importance of continuing to reanalyze ES even more than 3 years after the ES was performed. Last, we have not encountered other studies that investigated which patients have continued care with providers and associated characteristics. We would also re-emphasize the need for clearer guidelines for exome and variant reinterpretations that other studies have highlighted (Richardson et al., 2021; Robertson et al., 2022). As Leung et al. (2021), described, clinicians may have differing opinions and practices for implementing ES reanalysis. By having guidelines for when ES reanalysis should be initiated, we can standardize this across the field and clarify the process for patients as they navigate their genetic diagnostic journeys.

In examining the involvement of genetics providers in patient care, we found that a genetic counselor was also involved in the care of patients who underwent reanalysis more than 81% of the time. This highlights the role that geneticists and genetic counselors have in ordering ES and facilitating ES reanalysis. Given their involvement, it was interesting to see how few patients continue to follow with these providers at our institution. While understanding why these patients are not following with genetics providers is beyond the scope of our review, our data revealed that most of our patients were indeed provided specific information for when they should be following up with their ordering provider. At this time, we are not able to reanalyze results without patients being followed in our clinics. However, by adopting an automated

process, we could potentially have reanalyses performed periodically. This current study will also motivate future studies comparing the 2013–2016 period to other more recent periods, especially as exome sequencing ordering has increased institutionally in the last five to six years.

In situations in which a patient was reported to have ES or reanalysis but no report was found in the EMR, we did not attempt to determine if the patient originally had a physical chart. This reveals a gap in a patient's medical record as other providers may not be able to find the patient's genetic testing results and/or ES reanalyses. Without access to these records, we cannot determine the patient's original phenotype, test ordered, or test results. Furthermore, without a record of the testing results, other providers may assume the testing was not completed and could attempt to order the same test again. This is an inefficient use of resources for the patients, providers, laboratories, and healthcare system.

While we cannot conclude that providers did not discuss reanalysis with their patients, without documentation of this discussion we must assume this topic did not arise. This may indicate patients and families are being unaware of the option for reanalysis and may have contributed to the observed lack of follow-up. Documenting these discussions ultimately helps providers by ensuring best testing strategies are implemented. This is critical now that these tests are being ordered more frequently, and inefficient ordering practices place a potential strain on the healthcare system.

We also noted a statistically significant difference between the number of patients who did have a reanalysis with private vs. public insurance. Given the barriers that private insurance often presents with pre-authorization requirements and benefits investigations, this was surprising to us. In addition, this may be indicative of more subtle socioeconomic differences influencing patient care. Patients with private insurance likely acquired it through an employer, meaning they have additional access to time-off from work to attend appointments, may have a higher disposable income, and may have better access to transportation to attend appointments. While we cannot currently provide reanalyses to families who do not return to clinic, we also need to do our best to accommodate the availability of our families, and to frequently communicate the benefits and importance of following with their genetics providers.

Further, patient age was not associated with a higher likelihood of reanalysis. While our age range encompassed almost a full lifespan, the age at initial ES was not associated with an increased ES reanalysis. While 60% of those who did have reanalysis were older children, it is worth considering the potential importance of longitudinal data in performing a reanalysis. Longitudinal data provides unique information on developing phenotypes which allows for a more comprehensive review of variants. Age of onset for certain features and progression of the phenotype are extremely useful for determining a differential diagnosis. In addition, vital status was not a significant indicator of reanalysis. No patients, who had ES performed during their life, had a reanalysis of the data after their death. Despite genetic counselors being uniquely trained to approach genetic information in the context of difficult psychosocial situations, we are not seeing these families after the patient's passing. Efforts to remain engaged with these families after a patient's death may ultimately result in a molecular diagnosis for these patients and can provide the family with more accurate recurrence risks.

Our study provided a unique opportunity to review our ES and reanalysis process and revealed interesting results. This retrospective analysis allowed us to examine areas where our institution may improve patient care and improve efficiency in how we utilize genetic testing. We observed several interesting trends such as increased likelihood of reanalysis for those with private insurance and that a genetics provider was involved in all instances of reanalysis. However, our study was not designed to reveal the specific reasons for these trends.

Limitations of our study include the relatively small sample size, single institution resources, years examined, and unadjusted statistical analyses. While we wanted to perform a retrospective review, our timeframe includes years before genetic testing was readily covered or accessible to many of our families. This may reflect that our families have a more negative view of the genetics team due to the cost of testing or availability of testing previously compared to the ability to offer testing and get testing covered now. In addition, we could have examined data that is no longer reflective of our current institution's practices and patient demographics. Last, by not performing adjusted analyses, we may have missed confounding factors for certain variables. Our study does have several strengths which include that a single person performed the data collection, our studied timeframe allows for adequate time for reanalysis to have been performed, and it includes multiple years. The patient demographics are reflective of our institution and the patient populations that we serve.

As research continues to move forward, we may be able to determine the causes for some of these trends. Finally, as we continue to move forward with establishing the best genetic care for patients and clinical practice, it is important to frequently re-examine clinical practices and identify areas where change should take place. Using the information gained from this study, future research focusing on establishing ES reanalysis guidelines will be important and help guide providers to best patient care practices. In addition, larger studies that can further confirm the association between the likelihood of reanalysis with variables such as patients having private insurance will be important for identifying patient populations who may need extra support for the best genomic and precision medicine care that we can offer. By performing reviews such as this, we can ensure our system is as efficient as possible and improve patient care in all disciplines.

Data Availability

A full report of our data and our collection instrument can be found in the supplemental materials. Requests for data can be reviewed by the corresponding author.

Declarations

All authors report no competing interests.

Author Contributions

Erin Conboy, Kayla Treat, and Francesco Vetrini were responsible for the original conceptualization for this work. Lauren Rosier was responsible for refinement of the project, design of the study, data collection, and initial manuscript. Benjamin M. Helm provided the statistical analyses for this project. All authors were involved in designing the methodology, editing of the manuscript, and approval of the final draft.

Acknowledgements

We would like to thank the Indiana University Genetic Counseling Graduate Program for their support and facilitation of graduate student research.

Ethics Declaration

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). This study was approved by the Indiana University Institutional Review Board (IRB: #11120). This study was determined to be of “Exempt” status due to the secondary use of private health information. Given that this study is of minimal risk and no procedures requiring written consent outside of a research context, it was deemed exempt and provided a waiver for informed consent. All data was de-identified once it had been obtained from the medical record.

Conflicts of Interest

Lauren Rosier, Benjamin M. Helm, Francesco Vetrini, Kayla Treat, Amy Breman, and Erin Conboy declare no conflicts of interest.

References

1. Alfares, A., Aloraini, T., Subaie, L. A., Alissa, A., Qudsi, A. A., Alahmad, A.,.. . Alfadhel, M. (2018). Whole-genome sequencing offers additional but limited clinical utility compared with reanalysis of whole-exome sequencing. Genet Med, *20*(11), 1328–1333. doi:10.1038/gim.2018.41
2. Baker, S. W., Murrell, J. R., Nesbitt, A. I., Pechter, K. B., Balciuniene, J., Zhao, X.,.. . Santani, A. B. (2019). Automated Clinical Exome Reanalysis Reveals Novel Diagnoses. J Mol Diagn, *21*(1), 38–48. doi:10.1016/j.jmoldx.2018.07.008
3. Ewans, L. J., Schofield, D., Shrestha, R., Zhu, Y., Gayevskiy, V., Ying, K.,.. . Roscioli, T. (2018). Whole-exome sequencing reanalysis at 12 months boosts diagnosis and is cost-effective when applied early in Mendelian disorders. Genet Med, *20*(12), 1564–1574. doi:10.1038/gim.2018.39
4. Klee, E. W., Cousin, M. A., Pinto, E. V. F., Morales-Rosado, J. A., Macke, E. L., Jenkinson, W. G.,.. . Lazaridis, K. N. (2021). Impact of integrated translational research on clinical exome sequencing. Genet Med, *23*(3), 498–507. doi:10.1038/s41436-020-01005-9
5. Leung, M. L., Ji, J., Baker, S., Buchan, J. G., Sivakumaran, T. A., Krock, B. L.,.. . Santani, A. B. (2022). A Framework of Critical Considerations in Clinical Exome Reanalyses by Clinical and Laboratory

Standards Institute. J Mol Diagn, *24*(2), 177–188. doi:10.1016/j.jmoldx.2021.11.004

6. Liu, P., Meng, L., Normand, E. A., Xia, F., Song, X., Ghazi, A.,.. . Yang, Y. (2019). Reanalysis of Clinical Exome Sequencing Data. N Engl J Med, *380*(25), 2478–2480. doi:10.1056/NEJMc1812033
7. Manickam, K., McClain, M. R., Demmer, L. A., Biswas, S., Kearney, H. M., Malinowski, J.,.. . Hisama, F. M. (2021). Exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability: an evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG). Genet Med. doi:10.1038/s41436-021-01242-6
8. Meng, L., Pammi, M., Saronwala, A., Magoulas, P., Ghazi, A. R., Vetrini, F.,.. . Lalani, S. R. (2017). Use of Exome Sequencing for Infants in Intensive Care Units: Ascertainment of Severe Single-Gene Disorders and Effect on Medical Management. JAMA Pediatr, *171*(12), e173438. doi:10.1001/jamapediatrics.2017.3438
9. Moreno-De-Luca, A., Millan, F., Pesacreta, D. R., Elloumi, H. Z., Oetjens, M. T., Teigen, C.,.. . Martin, C. L. (2021). Molecular Diagnostic Yield of Exome Sequencing in Patients With Cerebral Palsy. Jama, *325*(5), 467–475. doi:10.1001/jama.2020.26148
10. PA Harris, R Taylor, R Thielke, J Payne, N Gonzalez, JG. Conde, Research electronic data capture (REDCap) – **A metadata-driven methodology and workflow process for providing translational research informatics support**, *J Biomed Inform. 2009 Apr;42(2):377 – 81.*
11. PA Harris, R Taylor, BL Minor, V Elliott, M Fernandez, L O'Neal, L McLeod, G Delacqua, F Delacqua, J Kirby, SN Duda, *REDCap Consortium*, *The REDCap consortium: Building an international community of software partners*, J Biomed Inform. 2019 *May 9 [doi*: 10.1016/j.jbi.2019.103208]
12. Richardson, B., Fitzgerald-Butt, S. M., Spoonamore, K. G., Wetherill, L., Helm, B. M., & Breman, A. M. (2021). Management of amended variant classification laboratory reports by genetic counselors in the United States and Canada: An exploratory study. J Genet Couns. doi:10.1002/jgc4.1514
13. Robertson, A. J., Tan, N. B., Spurdle, A. B., Metke-Jimenez, A., Sullivan, C., & Waddell, N. (2022). Re-analysis of genomic data: An overview of the mechanisms and complexities of clinical adoption. Genetics in medicine: official journal of the American College of Medical Genetics, 24(4), 798–810. https://doi.org/10.1016/j.gim.2021.12.011
14. Stark, Z., Schofield, D., Martyn, M., Rynehart, L., Shrestha, R., Alam, K.,.. . White, S. M. (2019). Does genomic sequencing early in the diagnostic trajectory make a difference? A follow-up study of clinical outcomes and cost-effectiveness. Genet Med, *21*(1), 173–180. doi:10.1038/s41436-018-0006-8
15. Wenger, A. M., Guturu, H., Bernstein, J. A., & Bejerano, G. (2017). Systematic reanalysis of clinical exome data yields additional diagnoses: implications for providers. Genet Med, *19*(2), 209–214. doi:10.1038/gim.2016.88
16. Yang, Y., Muzny, D. M., Xia, F., Niu, Z., Person, R., Ding, Y.,.. . Eng, C. M. (2014). Molecular findings among patients referred for clinical whole-exome sequencing. Jama, *312*(18), 1870–1879. doi:10.1001/jama.2014.14601

Figures

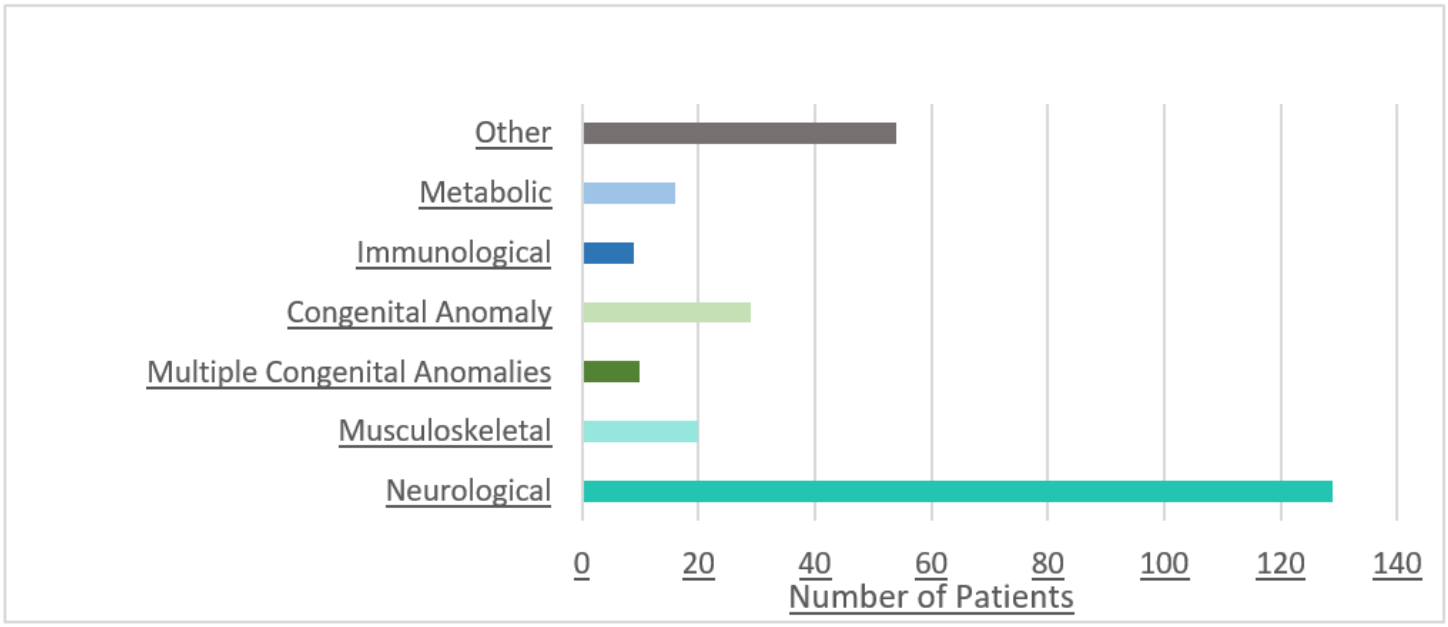

Figure 1

Patient indication for whole exome sequencing by most affected organ systems

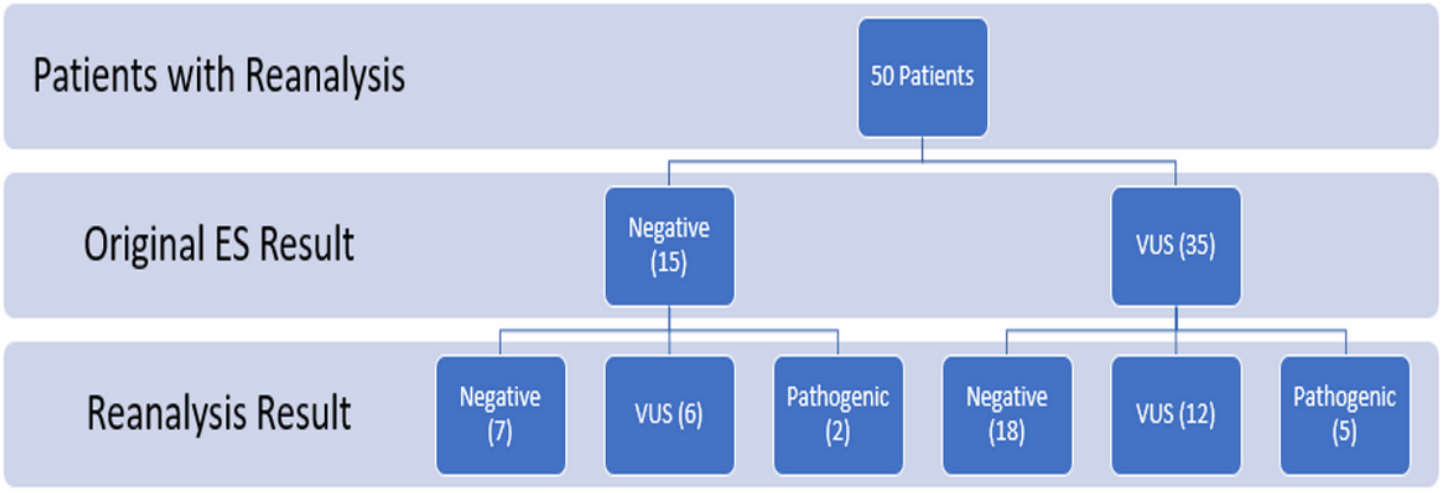

Figure 2

Description of ES results for patients who underwent reanalysis and the resulting reanalysis outcomes

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- DataFinal.csv

- ExomeReanalysisREDCapInstruments.pdf