

# FOR >>> FORWARD



40th Annual Conference  
September 22–26 > 2021

National Society of  
**Genetic** Counselors



# Can Expanded Carrier Screening Shorten the Diagnostic Odyssey in those with Genetic Disease?

*Presented by:*

**Maysen Mesaros, MS, CGC**  
*She/her/hers*

# FORWARD >>

40th Annual Conference > September 22-26 > 2021



National Society of  
**Genetic Counselors**

# Conflict of Interest Disclosure

- This study was conducted during an internship with Myriad Genetics, Inc.
- Maysen Mesaros had/has no financial interest in Myriad Genetics, Inc.
- Aishwarya Arjunan, Raul Torres, Rotem Ben-Shachar, Katie Johansen Taber were employed by Myriad Genetics, Inc. at the time of the study and received salary and stock options



## Co-authors

- Aishwarya Arjunan, MS, MPH, CGC, CPH
- Raul Torres, PhD
- Rotem Ben-Shachar, PhD
- Katie Johansen Taber, PhD



## Background: Whole Exome Sequencing

- Substantial proportion of serious pediatric disease are caused by rare monogenic disorders
- Growing number of pediatric diseases are diagnosed by whole exome sequencing (WES)
  - Analysis of protein-coding region of genes (~20,000)
- WES may be offered after chromosomal microarray, karyotype, multi-gene panel, biochemical testing
- WES Cost
  - Per Tan et. al 2017 WES cost analysis study
    - Cost per patient of the standard diagnostic pathway with WES was \$9792
    - WES performed at the first genetics appointment \$5347
  - Per Daga et. al 2018
    - Average commercial **cost of WES ranges from \$1,000-\$2,100 per sample in the United States**
- Standard Turn Around Time (TAT): 8-10 weeks



## Background: Expanded Carrier Screening

- Expanded carrier screening (ECS) identifies reproductive partners who are carriers of autosomal recessive (AR) or X-linked (XL) monogenic disorders
- Screens for severe disorders that typically affect quality of life at an early age
- Regardless of race, ethnicity, ancestry (REA)
- Average of **311** genes on ECS across four commercial laboratories
- Average TAT of 1-2 weeks



## Research Question

*If the parents of a child diagnosed by WES had undergone ECS, could they have received a diagnosis without needing WES?*



## Methods

- Literature search reporting WES in pediatric populations from October 2013 to January 2021
- Diagnoses and the associated genes identified were compared to genes on commercially-available ECS panels
  - Myriad Women's Health, Invitae, Integrated Genetics, and Sema4



## Methods

### Included studies

- Majority pediatric cohort
- Definitive diagnosis
- $\geq 1$  AR or XL diagnosis made
- Global cohorts
- Targeted/small cohorts and large non-targeted

### Excluded studies

- Re-analysis
- Genes not previously reported in humans
- Aggregate data only



## Results

- 28 cohorts reviewed
- Cohorts of 18 to 2,000 patients
- Previous testing performed in 21 cohorts
  - Microarray, karyotype, metabolic, panel sequencing, single gene tests
- Definitive diagnosis achieved in **40.1%** of patients
  - Autosomal dominant (AD), autosomal recessive (AR) and X-linked (XL)
    - **AD: 61.3%**
    - **AR: 31.4%**
    - **XL: 7.3%**



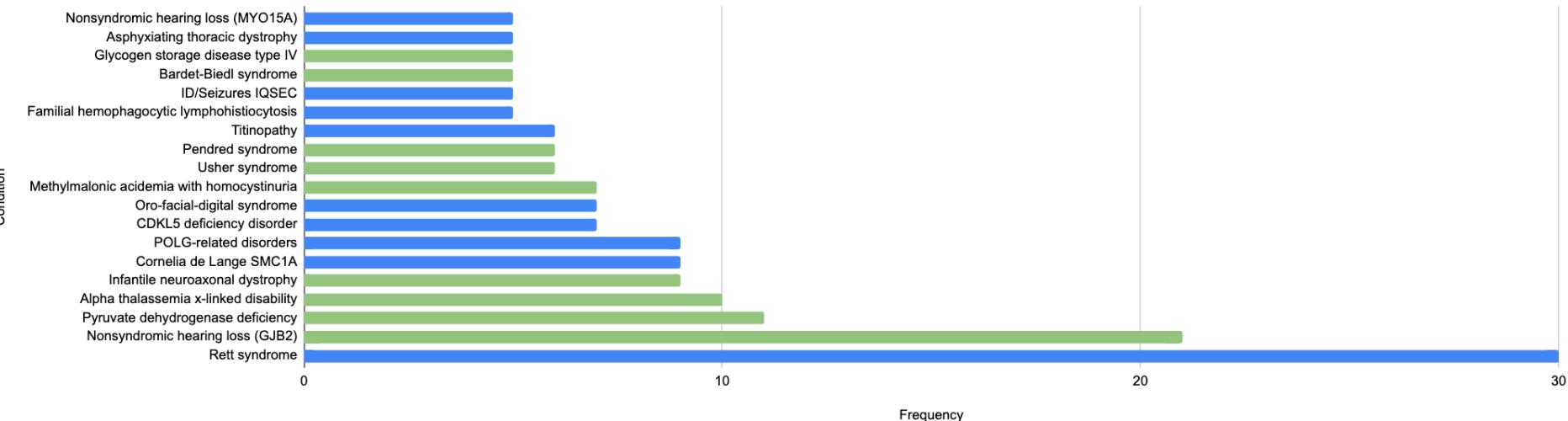
## Results

- Among the AR and XL conditions, **43.4%** are included on commonly ordered commercial ECS panels
- This implies that children whose parents had undergone ECS may have received a diagnosis without needing WES

## Common Conditions ( $\geq 5$ dx)

Condition	Frequency
Nonsyndromic hearing loss (MYO15A)	5
Asphyxiating thoracic dystrophy	5
ID/Seizures IQSEC	5
Glycogen storage disease type IV	5
Bardet-Biedl syndrome	5
Familial hemophagocytic lymphohistiocytosis	5
Pendred syndrome	6
Usher syndrome	6
Titinopathy	6
Methylmalonic acidemia with homocystinuria	7
Oro-facial-digital syndrome	7
CDKL5 deficiency disorder	7
POLG-related disorders	9
Cornelia de Lange SMC1A	9
Infantile neuroaxonal dystrophy	9
Alpha thalassemia x-linked disability	10
Pyruvate dehydrogenase deficiency	11
Nonsyndromic hearing loss (GJB2)	21
Rett syndrome	30

## Commonly Diagnosed Disorders



= ECS

- All ECS genes were found on >3 of the analyzed panels
  - Exception *PLA2G6*



## Tier 3 Carrier Screening

- Total AR and XL diagnoses = 1,042
- 150 are ACMG Tier 3 conditions
  - 14.%
- Tier 3 = ≥ 1/200 carrier frequency
- ACMG Recommends
  - All pregnant patients and those planning a pregnancy should be offered Tier 3 carrier screening



## Case Example

- 278 infants within the first 100 days of life
- Admitted to Texas Children's Hospital in Houston
- 190 (68.3%) NICU
- 43 (15.5%) CVICU
- 18 (6.5%) PICU
- Chromosomal microarray analysis (CMA) was completed in 237/278 (85%) infants



## Case Example Continued

- 57 AR or XL diagnoses (20.50%)
- 45.09% on ECS
- **AR:** NPHP3, HSD17B4, DYNC2H1 (x2), FANCA, UNC13D, ACAD9, LIPT1, KLHL40, SLC4A11, COL12A1, WNT5A, MUT, BRCA2, TRMU (x2), FAT4, ETFDH, ENPP1, GBE1(x2), WDR19, POMT2, GDF1, POMT1, VPS33B, TMEM67, RAG1, ALDH7A1, TTN, ATP8B1, ALG6, EARS2 (x2), SMAD6, BBS1, AGTR1, TBCD, ISPD, ODSL1, PRF1, WNT10B, ASPM
- **XL:** CDKL5, SHOX, PDHA1, LAS1L, OCRL, ATP7A, ARX, ABCD1, BCAP31, PLXNB3, MECP2, OFD1 (x3)

= ECS



## Familial hemophagocytic lymphohistiocytosis

- UNC13D gene, on ECS
- Body makes too many activated immune cells
  - Life threatening
    - Hepatosplenomegaly
    - Fever, rash
    - Lymph node enlargement
    - Kidney, heart, breathing, neurological problems
    - Increased risk for leukemia and lymphoma
- Treat with allogenic hematopoietic stem cell transplant
  - AS EARLY AS POSSIBLE!!
  - Without treatment, median survival <2-6 months after diagnosis



## Conclusion/Discussion

A large proportion of genes found by WES as causative of pediatric disease are included on ECS panels

*As WES often is a last resort after many other diagnostic tests, ECS screening, and the knowledge that it provides to parents about risk to their future children, may be useful in targeting and shortening the diagnostic odyssey for affected children*



## References

- Australian Genomics Health Alliance Acute Care Flagship, Lunke, S., Eggers, S., Wilson, M., Patel, C., Barnett, C. P., Pinner, J., Sandaradura, S. A., Buckley, M. F., Krzesinski, E. I., de Silva, M. G., Brett, G. R., Boggs, K., Mowat, D., Kirk, E. P., Adès, L. C., Akesson, L. S., Amor, D. J., Ayres, S., Baxendale, A., ... Stark, Z. (2020). Feasibility of Ultra-Rapid Exome Sequencing in Critically Ill Infants and Children With Suspected Monogenic Conditions in the Australian Public Health Care System. *JAMA*, 323(24), 2503–2511. <https://doi.org/10.1001/jama.2020.7671>
- Bademci, G., Foster, J., 2nd, Mahdieh, N., Bonyadi, M., Duman, D., Cengiz, F. B., Menendez, I., Diaz-Horta, O., Shirkavand, A., Zeinali, S., Subasioglu, A., Tokgoz-Yilmaz, S., Huesca-Hernandez, F., de la Luz Arenas-Sordo, M., Dominguez-Aburto, J., Hernandez-Zamora, E., Montenegro, P., Paredes, R., Moreta, G., Vinuela, R., ... Tekin, M. (2016). Comprehensive analysis via exome sequencing uncovers genetic etiology in autosomal recessive nonsyndromic deafness in a large multiethnic cohort. *Genetics in medicine : official journal of the American College of Medical Genetics*, 18(4), 364–371. <https://doi.org/10.1038/gim.2015.89>
- Daga, A., Majmundar, A. J., Braun, D. A., Gee, H. Y., Lawson, J. A., Shril, S., Jobst-Schwan, T., Vivante, A., Schapiro, D., Tan, W., Warejko, J. K., Widmeier, E., Nelson, C. P., Fathy, H. M., Gucev, Z., Soliman, N. A., Hashmi, S., Halbritter, J., Halty, M., Kari, J. A., ... Hildebrandt, F. (2018). Whole exome sequencing frequently detects a monogenic cause in early onset nephrolithiasis and nephrocalcinosis. *Kidney international*, 93(1), 204–213. <https://doi.org/10.1016/j.kint.2017.06.025>
- Demos, M., Guella, I., DeGuzman, C., McKenzie, M. B., Buerki, S. E., Evans, D. M., Toyota, E. B., Boelman, C., Huh, L. L., Datta, A., Michoulas, A., Selby, K., Bjornson, B. H., Horvath, G., Lopez-Rangel, E., van Karnebeek, C., Salvarinova, R., Slade, E., Eydoux, P., Adam, S., ... Farrer, M. J. (2019). Diagnostic Yield and Treatment Impact of Targeted Exome Sequencing in Early-Onset Epilepsy. *Frontiers in neurology*, 10, 434. <https://doi.org/10.3389/fneur.2019.00434>
- Dillon, O. J., Lunke, S., Stark, Z., Yeung, A., Thorne, N., Melbourne Genomics Health Alliance, Gaff, C., White, S. M., & Tan, T. Y. (2018). Exome sequencing has higher diagnostic yield compared to simulated disease-specific panels in children with suspected monogenic disorders. *European journal of human genetics : EJHG*, 26(5), 644–651. <https://doi.org/10.1038/s41431-018-0099-1>
- Dong, X., Liu, B., Yang, L., Wang, H., Wu, B., Liu, R., Chen, H., Chen, X., Yu, S., Chen, B., Wang, S., Xu, X., Zhou, W., & Lu, Y. (2020). Clinical exome sequencing as the first-tier test for diagnosing developmental disorders covering both CNV and SNV: a Chinese cohort. *Journal of medical genetics*, 57(8), 558–566. <https://doi.org/10.1136/jmedgenet-2019-106377>
- Downie, L., Halliday, J., Burt, R., Lunke, S., Lynch, E., Martyn, M., Poulakis, Z., Gaff, C., Sung, V., Wake, M., Hunter, M. F., Saunders, K., Rose, E., Lewis, S., Jarmolowicz, A., Phelan, D., Rehm, H. L., Melbourne Genomics Health Alliance, & Amor, D. J. (2020). Exome sequencing in infants with congenital hearing impairment: a population-based cohort study. *European journal of human genetics : EJHG*, 28(5), 587–596. <https://doi.org/10.1038/s41431-019-0553-8>
- Farwell, K. D., Shahmirzadi, L., El-Khechen, D., Powis, Z., Chao, E. C., Tippin Davis, B., Baxter, R. M., Zeng, W., Mroske, C., Parra, M. C., Gandomi, S. K., Lu, I., Li, X., Lu, H., Lu, H. M., Salvador, D., Ruble, D., Lao, M., Fischbach, S., Wen, J., ... Tang, S. (2015). Enhanced utility of family-centered diagnostic exome sequencing with inheritance model-based analysis: results from 500 unselected families with undiagnosed genetic conditions. *Genetics in medicine : official journal of the American College of Medical Genetics*, 17(7), 578–586. <https://doi.org/10.1038/gim.2014.154>
- Gregg AR, Aarabi M, Klugman S, et al. Screening for autosomal recessive and X-linked conditions during pregnancy and preconception: a practice resource of the American College of Medical Genetics and Genomics (ACMG) [published online ahead of print, 2021 Jul 20] [published correction appears in Genet Med. 2021 Aug 27;]. *Genet Med.* 2021;10:1038/s41436-021-01203-z. doi:10.1038/s41436-021-01203-z



## References

- Iglesias, A., Anyane-Yeboa, K., Wynn, J., Wilson, A., Truitt Cho, M., Guzman, E., Sisson, R., Egan, C., & Chung, W. K. (2014). The usefulness of whole-exome sequencing in routine clinical practice. *Genetics in medicine : official journal of the American College of Medical Genetics*, 16(12), 922–931. <https://doi.org/10.1038/gim.2014.58>
- Kingsmore, S. F., Cakici, J. A., Clark, M. M., Gaughran, M., Feddock, M., Batalov, S., Bainbridge, M. N., Carroll, J., Taylor, S. A., Clarke, C., Ding, Y., Ellsworth, K., Farnaes, L., Hildreth, A., Hobbs, C., James, K., Kint, C. I., Lenberg, J., Nahas, S., Prince, L., ... RCIGM Investigators (2019). A Randomized, Controlled Trial of the Analytic and Diagnostic Performance of Singleton and Trio, Rapid Genome and Exome Sequencing in III Infants. *American journal of human genetics*, 105(4), 719–733. <https://doi.org/10.1016/j.ajhg.2019.08.009>
- Kuperberg, M., Lev, D., Blumkin, L., Zerem, A., Ginsberg, M., Linder, I., Carmi, N., Kivity, S., Lerman-Sagie, T., & Leshinsky-Silver, E. (2016). Utility of Whole Exome Sequencing for Genetic Diagnosis of Previously Undiagnosed Pediatric Neurology Patients. *Journal of child neurology*, 31(14), 1534–1539. <https://doi.org/10.1177/0883073816664836>
- Lazaridis, K. N., Schahl, K. A., Cousin, M. A., Babovic-Vuksanovic, D., Riegert-Johnson, D. L., Gavrilova, R. H., McAllister, T. M., Lindor, N. M., Abraham, R. S., Ackerman, M. J., Pichurin, P. N., Deyle, D. R., Gavrilov, D. K., Hand, J. L., Klee, E. W., Stephens, M. C., Wick, M. J., Atkinson, E. J., Linden, D. R., Ferber, M. J., ... Individualized Medicine Clinic Members (2016). Outcome of Whole Exome Sequencing for Diagnostic Odyssey Cases of an Individualized Medicine Clinic: The Mayo Clinic Experience. *Mayo Clinic proceedings*, 91(3), 297–307. <https://doi.org/10.1016/j.mayocp.2015.12.018>
- Lee, H., Deignan, J. L., Dorrani, N., Strom, S. P., Kantarci, S., Quintero-Rivera, F., Das, K., Toy, T., Harry, B., Yourshaw, M., Fox, M., Fogel, B. L., Martinez-Agosto, J. A., Wong, D. A., Chang, V. Y., Shieh, P. B., Palmer, C. G., Dipple, K. M., Grody, W. W., Vilain, E., ... Nelson, S. F. (2014). Clinical exome sequencing for genetic identification of rare Mendelian disorders. *JAMA*, 312(18), 1880–1887. <https://doi.org/10.1001/jama.2014.14604>
- Mahfouz, N. A., Kizhakkedath, P., Ibrahim, A., El Naofal, M., Ramaswamy, S., Harilal, D., Qutub, Y., Uddin, M., Taylor, A., Alloub, Z., AlBanna, A., Abuhammour, W., Fathalla, B., & Tayoun, A. A. (2020). Utility of clinical exome sequencing in a complex Emirati pediatric cohort. *Computational and structural biotechnology journal*, 18, 1020–1027. <https://doi.org/10.1016/j.csbj.2020.04.013>
- Mahler, E. A., Johannsen, J., Tsiakas, K., Kloth, K., Lüttgen, S., Mühlhausen, C., Alhaddad, B., Haack, T. B., Strom, T. M., Kortüm, F., Meitinger, T., Muntau, A. C., Santer, R., Kubisch, C., Lessel, D., Denecke, J., & Hempel, M. (2019). Exome Sequencing in Children. *Deutsches Arzteblatt international*, 116(12), 197–204. <https://doi.org/10.3238/arztebl.2019.0197>
- Meng, L., Pammi, M., Saronwala, A., Magoulas, P., Ghazi, A. R., Vetrini, F., Zhang, J., He, W., Dharmadhikari, A. V., Qu, C., Ward, P., Braxton, A., Narayanan, S., Ge, X., Tokita, M. J., Santiago-Sim, T., Dai, H., Chiang, T., Smith, H., Azamian, M. S., ... 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 pediatrics*, 171(12), e173438. <https://doi.org/10.1001/jamapediatrics.2017.3438>
- Nolan, D., & Carlson, M. (2016). Whole Exome Sequencing in Pediatric Neurology Patients: Clinical Implications and Estimated Cost Analysis. *Journal of child neurology*, 31(7), 887–894. <https://doi.org/10.1177/0883073815627880>
- Quiao, C., Moreira, C. M., Novo-Filho, G. M., Sacramento-Bobotis, P. R., Groenner Penna, M., Perazzio, S. F., Dutra, A. P., da Silva, R. A., Santos, M., de Arruda, V., Freitas, V. G., Pereira, V. C., Pintao, M. C., Fornari, A., Buzolin, A. L., Oku, A. Y., Burger, M., Ramalho, R. F., Marco Antonio, D. S., E Ferreira, E. N., ... Baratela, W. (2020). Diagnostic power and clinical impact of exome sequencing in a cohort of 500 patients with rare diseases. *American journal of medical genetics. Part C, Seminars in medical genetics*, 184(4), 955–964. <https://doi.org/10.1002/ajmg.c.31860>
- U.S. Department of Health and Human Services. (n.d.). *Familial hemophagocytic lymphohistiocytosis*. Genetic and Rare Diseases Information Center. <https://rarediseases.info.nih.gov/diseases/6589/familial-hemophagocytic-lymphohistiocytosis>.

## References

- Śmigiel, R., Biela, M., Szymd, K., Bloch, M., Szmida, E., Skiba, P., Walczak, A., Gasperowicz, P., Kosińska, J., Rydzanicz, M., Stawiński, P., Biernacka, A., Zielińska, M., Gołębiowski, W., Jalowska, A., Ohia, G., Głowska, B., Walas, W., Królik-Olejnik, B., Krajewski, P., ... Płoski, R. (2020). Rapid Whole-Exome Sequencing as a Diagnostic Tool in a Neonatal/Pediatric Intensive Care Unit. *Journal of clinical medicine*, 9(7), 2220. <https://doi.org/10.3390/jcm9072220>
- Srivastava, S., Cohen, J. S., Vernon, H., Barañano, K., McClellan, R., Jamal, L., Naidu, S., & Fatemi, A. (2014). Clinical whole exome sequencing in child neurology practice. *Annals of neurology*, 76(4), 473–483. <https://doi.org/10.1002/ana.24251>
- Stark, Z., Tan, T. Y., Chong, B., Brett, G. R., Yap, P., Walsh, M., Yeung, A., Peters, H., Mordaunt, D., Cowie, S., Amor, D. J., Savarirayan, R., McGillivray, G., Downie, L., Ekert, P. G., Theda, C., James, P. A., Yaplito-Lee, J., Ryan, M. M., Leventer, R. J., ... White, S. M. (2016). A prospective evaluation of whole-exome sequencing as a first-tier molecular test in infants with suspected monogenic disorders. *Genetics in medicine : official journal of the American College of Medical Genetics*, 18(11), 1090–1096. <https://doi.org/10.1038/gim.2016.1>
- Tan, T. Y., Dillon, O. J., Stark, Z., Schofield, D., Alam, K., Shrestha, R., Chong, B., Phelan, D., Brett, G. R., Creed, E., Jarmolowicz, A., Yap, P., Walsh, M., Downie, L., Amor, D. J., Savarirayan, R., McGillivray, G., Yeung, A., Peters, H., Robertson, S. J., ... White, S. M. (2017). Diagnostic Impact and Cost-effectiveness of Whole-Exome Sequencing for Ambulant Children With Suspected Monogenic Conditions. *JAMA pediatrics*, 171(9), 855–862. <https://doi.org/10.1001/jamapediatrics.2017.1755>
- Valencia, C. A., Husami, A., Holle, J., Johnson, J. A., Qian, Y., Mathur, A., Wei, C., Indugula, S. R., Zou, F., Meng, H., Wang, L., Li, X., Fisher, R., Tan, T., Hogart Begtrup, A., Collins, K., Wusik, K. A., Neilson, D., Burrow, T., Schorry, E., ... Zhang, K. (2015). Clinical Impact and Cost-Effectiveness of Whole Exome Sequencing as a Diagnostic Tool: A Pediatric Center's Experience. *Frontiers in pediatrics*, 3, 67. <https://doi.org/10.3389/fped.2015.00067>
- Vissers, L., van Nimwegen, K., Schieving, J. H., Kamsteeg, E. J., Kleefstra, T., Yntema, H. G., Pfundt, R., van der Wilt, G. J., Krabbenborg, L., Brunner, H. G., van der Burg, S., Grutters, J., Veltman, J. A., & Willemsen, M. (2017). A clinical utility study of exome sequencing versus conventional genetic testing in pediatric neurology. *Genetics in medicine : official journal of the American College of Medical Genetics*, 19(9), 1055–1063. <https://doi.org/10.1038/gim.2017.1>
- Wang, H., Qian, Y., Lu, Y., Qin, Q., Lu, G., Cheng, G., Zhang, P., Yang, L., Wu, B., & Zhou, W. (2020). Clinical utility of 24-h rapid trio-exome sequencing for critically ill infants. *NPJ genomic medicine*, 5, 20. <https://doi.org/10.1038/s41525-020-0129-0>
- Yang, Y., Muzny, D. M., Xia, F., Niu, Z., Person, R., Ding, Y., Ward, P., Braxton, A., Wang, M., Buhay, C., Veeraraghavan, N., Hawes, A., Chiang, T., Leduc, M., Beuten, J., Zhang, J., He, W., Scull, J., Willis, A., Landsverk, M., ... Eng, C. M. (2014). Molecular findings among patients referred for clinical whole-exome sequencing. *JAMA*, 312(18), 1870–1879. <https://doi.org/10.1001/jama.2014.14601>
- Yang, Y., Muzny, D. M., Reid, J. G., Bainbridge, M. N., Willis, A., Ward, P. A., Braxton, A., Beuten, J., Xia, F., Niu, Z., Hardison, M., Person, R., Bekheirnia, M. R., Leduc, M. S., Kirby, A., Pham, P., Scull, J., Wang, M., Ding, Y., Plon, S. E., ... Eng, C. M. (2013). Clinical whole-exome sequencing for the diagnosis of mendelian disorders. *The New England journal of medicine*, 369(16), 1502–1511. <https://doi.org/10.1056/NEJMoa1306555>
- Zhu, X., Petrovski, S., Xie, P., Ruzzo, E. K., Lu, Y. F., McSweeney, K. M., Ben-Zeev, B., Nissenkorn, A., Anikster, Y., Oz-Levi, D., Dhindsa, R. S., Hitomi, Y., Schoch, K., Spillmann, R. C., Heimer, G., Marek-Yagel, D., Tzadok, M., Han, Y., Worley, G., Goldstein, J., ... Goldstein, D. B. (2015). Whole-exome sequencing in undiagnosed genetic diseases: interpreting 119 trios. *Genetics in medicine : official journal of the American College of Medical Genetics*, 17(10), 774–781. <https://doi.org/10.1038/gim.2014.191>



**Thank you!**  
**Questions/Comments:**  
**[mesaros@musc.edu](mailto:mesaros@musc.edu)**