A clinical laboratory's experience using GeneMatcher – building stronger gene-disease relationships.

Julie Taylor[1], Alka Malhotra[2], Nicole Burns[1], Amanda Clause[1], Carolyn Brown[1], Brendan Burns[1], Anjana Chandrasekhar[1], Zina Schlachetzki[1], Maren Bennett[1], Erin Thorpe[1], Ryan Taft[2], Denise Perry[2], and Alison Coffey[1]

[1]Illumina Inc
[2]Illumina Inc.

February 22, 2024

Abstract

The use of whole-genome sequencing (WGS) has accelerated the pace of gene discovery and highlighted the need for open and collaborative data sharing in the search for novel disease genes and variants. GeneMatcher (GM) is designed to facilitate connections between researchers, clinicians, health-care providers and others to help in the identification of additional patients with variants in the same candidate disease genes. The Illumina Clinical Services Laboratory offers a WGS test for patients with suspected rare and undiagnosed genetic disease and regularly submits potential candidate genes to GM to strengthen gene-disease relationships. We describe our experience with GM, including criteria for evaluation of candidate genes, and our workflow for the submission and review process. We have made 69 submissions, 36 of which are currently active. Ten per cent of submissions have resulted in publications, with an additional 14 submissions part of ongoing collaborations and expected to result in a publication.

A clinical laboratory's experience using GeneMatcher – building stronger gene-disease relationships.

Julie P. Taylor, Alka Malhotra, Nicole J. Burns, Amanda R. Clause, Carolyn M. Brown, Brendan T. Burns, Anjana Chandrasekhar, Zina Schlachetzki, Maren Bennett, Erin Thorpe, Ryan J. Taft, Denise L. Perry, Alison J. Coffey.

Medical Genomics Research, Illumina Inc., 5200 Illumina Way, San Diego, CA 92122, USA

Abstract:

The use of whole-genome sequencing (WGS) has accelerated the pace of gene discovery and highlighted the need for open and collaborative data sharing in the search for novel disease genes and variants. GeneMatcher (GM) is designed to facilitate connections between researchers, clinicians, health-care providers and others to help in the identification of additional patients with variants in the same candidate disease genes. The Illumina Clinical Services Laboratory offers a WGS test for patients with suspected rare and undiagnosed genetic disease and regularly submits potential candidate genes to GM to strengthen gene-disease relationships. We describe our experience with GM, including criteria for evaluation of candidate genes, and our workflow for the submission and review process. We have made 69 submissions, 36 of which are currently active. Ten per cent of submissions have resulted in publications, with an additional 14 submissions part of ongoing collaborations and expected to result in a publication.

Keywords: whole-genome sequencing; data sharing; rare disease; gene-disease relationship; GeneMatcher; gene discovery

Whole-genome sequencing (WGS) is a comprehensive genetic test that is emerging as a first-tier diagnostic test for patients with rare and undiagnosed genetic disease (RUGD) (Bertoli-Avella et al., 2021; Lionel et al., 2018; NICUSeq Study Group et al., 2021; Scocchia et al., 2019; Turro et al., 2020). Diagnostic rates are estimated at between 20% and 68% depending on the study population, inclusion criteria, and comprehensiveness of the test (Dimmock et al., 2021; French et al., 2019; NICUSeq Study Group et al., 2021; Scocchia et al., 2019), meaning that even after WGS testing, some cases remain unsolved. While the use of genome sequencing has accelerated the pace of gene discovery (Bamshad et al., 2019), for many rare genetic diseases, the scientific literature is restricted to only one or maybe a handful of families with affected individuals, making clinical interpretation and reporting of potentially relevant variant data difficult due to the limited evidence of the relationship between the gene and the disease. For clinicians and researchers, it can be time- and resource-intensive to gather sufficient evidence to publish individual families as case reports, and therefore these cases may go unreported. Open and collaborative data sharing is thus essential in the search for, and confirmation of, novel disease genes and variants.

The Illumina Clinical Services Laboratory is a Clinical Laboratory Improvement Amendments (CLIA)-certified, College of American Pathologists (CAP)-approved clinical laboratory offering WGS for patients with a suspected rare and undiagnosed genetic disease. The WGS test includes an assessment of single nucleotide variants, indels, copy number variants, mitochondrial single nucleotide variants, select repeat expansions, and spinal muscular atrophy status. The majority of cases have a trio family structure (parents and affected child), with other family structures supported including duos (parent and child), higher-order family structures (e.g., quad) and proband-only. Cases analyzed in the laboratory are primarily from a pediatric population but also include adults with an indication for testing for RUGD (NICUSeq Study Group et al., 2021; Scocchia et al., 2019; Vanderver et al., 2020). During the course of case analysis, all variants meeting specific variant filtering criteria are reviewed across all genes in the genome that meet coverage and mapping quality metrics. Genes that lack sufficient evidence of a relationship to human genetic disease but have some evidence to suggest a potential association or relevance to the patient being tested are identified through this analysis. Here, we describe our clinical laboratory's process and experience to date in submitting candidate genes to GeneMatcher (GM) (Sobreira et al., 2015), a node of the Matchmaker Exchange (MME) (Azzariti & Hamosh, 2020).

The laboratory considers submitting a gene to GM if no diagnostic variant was identified in the patient tested or if the variants identified do not fully explain the patient's phenotype. Before a candidate gene is submitted to GM, evidence supporting a potential gene-disease relationship (GDR) is gathered from the literature or publicly available variant or gene databases (e.g., ClinVar; Landrum et al., (2018); DECIPHER (Firth et al., 2009); The Clinical Genome Resource (ClinGen; https://clinicalgenome.org/curation-activities/gene-disease-validity/); The Gene Curation Coalition (GenCC; https://thegencc.org/); Mouse Genome Informatics (MGI; Blake et al., (2021) and evaluated using the ClinGen gene disease validity curation process (Strande et al., 2017). This gene-level evidence, and the characteristics of the identified variant in the context of the patient being tested, are evaluated against a set of internally developed minimum criteria created to ensure consistency across laboratory analysts in the identification of strong candidates likely to result in successful matches (Figure 1). Variants are checked for call quality, allele frequency in the Genome Aggregation Database (gnomAD) (Karczewski et al., 2020), potential to be disease-causing in the patient based on phenotype information, variant consequence and inheritance, and occurrence in a gene without an established GDR. Candidate genes with a well-established GDR may be submitted if the proband's phenotypic presentation differs from that reported in the literature to explore a potential expansion of phenotype or a new GDR. Genes may also be submitted if the inheritance pattern in the proband differs from that described in the literature.

Our clinical laboratory's internal workflow, from identification of candidate genes through submission, follow-up, and review of ongoing submissions is illustrated in Figure 2. Ordering physicians are notified of any possible collaborations to prevent duplicate submissions that could result in self-matches and to ensure any necessary additional patient consent is obtained. In this workflow, laboratory personnel facilitate collaborations and initiate the connection between researchers and clinicians with ongoing support as required.

Submissions are reviewed on a quarterly basis to determine if any actions are required. In this review, a literature search for the gene is performed to identify any new clinical or experimental evidence supporting the GDR. Evidence in publicly available databases is also reviewed. Following review, next steps may include prioritization of matches for more proactive follow up, recuration of the GDR (if new literature has been identified), and/or suspension of a submission. Submissions may be suspended for a variety of reasons (see below) and are excluded from matching with other submissions but may be reactivated at any time.

Table 1 provides a summary of our submissions to GM from 2016 to date. In total we have made 69 submissions over the six year time period. From September 2020 through September 2021, since implementation of the minimum criteria, 508 RUGD cases were sequenced through our laboratory. Of these, variants were reported in 325 cases (64%), with 183 cases (36%) having no variants identified that are of likely relevance to the clinical indications for the test. During this time period, 13 submissions were made to GM.

At the time of this publication, we have 36 active submissions in GM, corresponding to 36 unique genes from 36 unrelated families. The majority of submissions involve genes in which missense variants, with nearly half of these variants occurring in a *de novo* state. Twenty-five submissions predate our minimum criteria but were reviewed upon implementation of the criteria to ensure they were still considered strong submissions. Fourteen of the 36 submissions are part of active ongoing collaborations at different stages of clinical and functional evidence gathering; all of these are expected to result in a publication. The earliest submission that is part of an ongoing collaboration is from August 2018, and the most recent from July 2021. At least nine of the genes involved in collaborations have 10 or more matches in either GM or MME, with a range from two to 69.

Twenty-two of our submissions are not currently part of an active collaboration. However, 19 of the 22 have matches, ranging in number from four to 33 (with an average of 14), all with potential for follow-up. For 10 of the 22 submissions, the patient's phenotype matched that of cases in the literature, and submissions were made to GM with the aim of identifying additional individuals with a similar phenotype or to explore a possible expansion of phenotype. In one example, a*de novo* heterozygous missense variant was identified in a patient whose phenotype did not overlap the typical presentation for single nucleotide variants reported in the literature. However, the patient's phenotype did overlap the phenotype seen in a mouse model which defined a critical region for a deletion syndrome, and one other affected individual in the literature. In another example, missense variants were reported in the literature in either a homozygous or compound heterozygous state in individuals whose phenotype overlapped our patient's phenotype, in whom we had also identified a compound heterozygous pair of variants. However, no evidence of gene impact was provided for any of the reported variants resulting in a limited classification for the GDR. Experimental support was available at the gene level, but additional clinical data were needed to strengthen the GDR and potentially upgrade the variant classification from a variant of uncertain significance (VUS).

For 12 of the 22 submissions, there was no phenotypic overlap between the patient and previously published cases, but the gene met our criteria for submission based on the characteristics of the case, the GDR, and the variant identified in the patient. In one instance, no clinical data had been reported in the literature but both expression data and two strong mouse models were consistent with the patient's phenotype. The GDR was classified as "no known disease relationship – animal model only", and the gene submitted to GM with the goal of identifying probands with a similar phenotype. In another instance, a homozygous missense variant classified as VUS, was identified in a patient who presented with a severe, atypical phenotype which was not yet well described in the literature. There was sufficient support for the GDR to be classified as definitive. In this instance, the submission was made to explore whether additional cases with a similar phenotype exist and could indicate the expansion of the phenotypic spectrum of this disease.

For six of the 22 GM submissions, variants were reported to the ordering clinician as variants of uncertain significance in genes of uncertain significance based on the limited available evidence for the GDR. For the remaining 15 submissions, variants were not considered to meet our current reporting criteria.

We have suspended 33 submissions: seven were suspended due to the matches resulting in a publication;

twelve were suspended as a result of publication of new evidence potentially impacting the classification of the GDR; two were suspended based on updated frequency data from gnomAD suggesting the variant in the candidate gene was unlikely to be disease-causing; and twelve were suspended due to being legacy submissions and no longer considered strong candidates.

To date, seven submissions involving cases analyzed by the Illumina Clinical Services Laboratory led to collaborations that resulted in publications (see Table 2). In three instances, (*USP7, SPEN,* and*AMMECR1*), the evidence published through the GM collaboration established a new disease gene and resulted in recuration of, and subsequent upgrade in the classification of the GDR. This in turn led to recuration of the associated variants and a change in variant classification from a variant of uncertain significance (previously reported as a research candidate) to a classification of likely pathogenic, thereby allowing reporting as a potential diagnostic finding in an amended report.

In the instance of *USP7* , Hao et al.,(2015) previously reported six cases with heterozygous chromosomal microdeletions, and one case with a heterozygous nonsense variant in individuals with a neurodevelopmental phenotype, suggesting haploinsufficiency of*USP7* as a disease mechanism. The microdeletions could not be scored using the ClinGen framework (Strande et al., 2017), hence the GDR was classified as limited. As a result of the collaboration established through GM, Fountain et al., (2019) reported 15 newly identified unrelated cases with a similar phenotype carrying heterozygous *de novo USP7* variants, including partial and full gene deletions, missense, frameshift, nonsense and canonical splice site variants. These data allowed an upgrade in classification of the GDR from limited to definitive, as well as an upgrade in classification of the variant identified in our patient.

The *SPEN* gene was identified as a strong candidate for GM because if its location within the critical region for the well-described 1p36 deletion syndrome and phenotypic overlap of the patient with the deletion syndrome. At the point of submission to GM, no cases had been identified in the literature with causal variants in *SPEN* , hence the GDR was classified as no known disease relationship. Based on the collaboration established through GM, Radio et al., (2021) reported 32 unrelated individuals, all with truncating loss of function variants, most of which were *de novo* . The GDR was reclassified as strong, pending replication of the association over time.

The *AMMECR1* gene is located within the Alport syndrome, mental retardation, midface hypoplasia, and elliptocytosis complex interval, which is associated with an Xq22.3 contiguous gene deletion syndrome encompassing about 20 genes. Prior to the GM publication, only two single nucleotide variants had been reported in the *AMMECR1* gene, (one nonsense and one missense). A submission was made to GM based on phenotypic overlap between our patient and the deletion syndrome, and variant type. Subsequently through a GM collaboration, Moysés-Oliveira et al., (2018) described five individuals with predicted loss of function variants in the *AMMECR1* gene presenting with short stature, cardiac and skeletal abnormalities, and hearing loss, with a similar presentation to the patient. These data supported the involvement of *AMMECR1* in a new syndrome with an expanded phenotype.

In the case of *GRIA3* (located on the X chromosome), the publication arising from the GM collaboration resulted in additional evidence allowing an upgrade in variant classification and resulting in issuing of an amended report. A notable aspect of this case is its contribution to the understanding of potential phenotypic manifestation and mechanism of disease in females, where previously variants had only been reported in association with a neurodevelopmental phenotype in males. Functional studies in cell culture models provided evidence that a gain of function and increased synaptic transmission may cause the epileptic encephalopathy and developmental delay seen in the affected female patient (Sun et al., 2021).

For three GDRs, *AGMO* with *AGMO* -related neurodevelopmental disorder (Okur et al., 2019), *LMBRD2* with *LMBRD2* -related neurodevelopmental disorder (Malhotra et al., 2021), and *CAMK4*with *CAMK4* -related neurodevelopmental disorder with dystonia and chorea (Zech et al., 2021), the additional evidence in the GM publication was insufficient to result in an upgrade to the classification of the GDR or variant at this time. For *CAMK4* and*AGMO,* the publications contained only one or two case reports, respectively.

For *LMBRD2,* while ten *de novo* missense variants including at least three recurrent variants were reported, functional studies were not performed so these were without experimental support of gene impact and so did not score highly in the ClinGen framework for gene curation (Strande et al., 2017).

Overall, submission to GM has been invaluable in our clinical laboratory for the discovery of new GDRs and in the confirmation of diagnostic variants in patients tested through WGS. In total we have made over 69 submissions from 2016 to 2021, 10% of which have resulted in publications of new disease genes, with a further 20% in ongoing collaborations.

As a clinical laboratory, a number of challenges apply to all aspects of data sharing, including through GM. These include the time required to prepare the data for sharing, updating data shared in external sources, and time for follow-up of queries and collaborations. To help address these challenges, we have developed an internal workflow and tracking system which restricts submissions to strong candidates and allows for easy review of submissions to maximize efforts. Our review process has proved valuable to keep submissions, and hence the content of GM, relevant by removing submissions that have been published or are in a firmly established collaboration, and to serve as a flag for reanalysis of GDRs when new data are available.

The time taken from GM submission to publication can be lengthy and varied considerably, from eight months to almost four years, with an average of just under 26 months. Factors that contribute to variability in GM submission to publication time include: the maturity of an ongoing collaboration (data gathering vs. manuscript already in preparation), difficulty in finding collaborations with the ability to perform functional studies, resource limitations, and challenges in case follow-up including the impracticality of obtaining additional consent from families who may not have already consented for research, who may be located in remote areas, or who may be lost to follow-up. Resources for functional studies can also be problematic, hence the importance of centralized functional data sets including those for model organisms. To facilitate data sharing in a more timely fashion, researchers and publishers could consider moving towards publication of aggregated case data without the requirement of experimental support to allow more rapid publication of a new GDR. Alternatively, ways of sharing data publically within GM could be explored to allow clinical laboratories visualization of new potential GDRs to aid in clinical reporting and maximizing return to the patients.

Taking all challenges into account, the value of data sharing via GM cannot be overstated, as demonstrated by the number of citations of GM (over 504) and novel gene-disease discoveries facilitated by GM to date (over 209) (Azzariti & Hamosh, 2020). Acceleration of gene discovery only serves to help deliver the full promise of WGS, particularly for individuals with rare disease, whose chance of receiving a potentially informative finding should not be constrained by the absence of large numbers of previously described cases.

Acknowledgements: We would like to acknowledge the ICSL Interpretation and Reporting Team and the Illumina Clinical Services Laboratory team for sequencing and bioinformatics support.

Conflicts of Interest Disclosure: All authors are employees and shareholders of Illumina Inc.

Data Availability Statement: Some of the data supporting this study are published and therefore publicly available. Other data that support the findings of this study are available from the corresponding author upon reasonable request.

References:

Azzariti, D. R., & Hamosh, A. (2020). Genomic Data Sharing for Novel Mendelian Disease Gene Discovery: The Matchmaker Exchange. *Annual Review of Genomics and Human Genetics* , *21* , 305–326. https://doi.org/10.1146/annurev-genom-083118-014915

Bamshad, M. J., Nickerson, D. A., & Chong, J. X. (2019). Mendelian Gene Discovery: Fast and Furious with No End in Sight. *American Journal of Human Genetics* , *105* (3), 448–455. https://doi.org/10.1016/j.ajhg.2019.07.011

Bertoli-Avella, A. M., Beetz, C., Ameziane, N., Rocha, M. E., Guatibonza, P., Pereira, C., Calvo, M., Herrera-Ordonez, N., Segura-Castel, M., Diego-Alvarez, D., Zawada, M., Kandaswamy, K. K., Werber, M., Paknia, O., Zielske, S., Ugrinovski, D., Warnack, G., Kampe, K., Iurașcu, M.-I., ... Bauer, P. (2021). Successful application of genome sequencing in a diagnostic setting: 1007 index cases from a clinically heterogeneous cohort. *European Journal of Human Genetics: EJHG* , *29* (1), 141–153. https://doi.org/10.1038/s41431-020-00713-9

Blake, J. A., Baldarelli, R., Kadin, J. A., Richardson, J. E., Smith, C. L., Bult, C. J., & Mouse Genome Database Group. (2021). Mouse Genome Database (MGD): Knowledgebase for mouse-human comparative biology.*Nucleic Acids Research* , *49* (D1), D981–D987. https://doi.org/10.1093/nar/gkaa1083

Dimmock, D., Caylor, S., Waldman, B., Benson, W., Ashburner, C., Carmichael, J. L., Carroll, J., Cham, E., Chowdhury, S., Cleary, J., D'Harlingue, A., Doshi, A., Ellsworth, K., Galarreta, C. I., Hobbs, C., Houtchens, K., Hunt, J., Joe, P., Joseph, M., ... Farnaes, L. (2021). Project Baby Bear: Rapid precision care incorporating rWGS in 5 California children's hospitals demonstrates improved clinical outcomes and reduced costs of care. *American Journal of Human Genetics* ,*108* (7), 1231–1238. https://doi.org/10.1016/j.ajhg.2021.05.008

Firth, H. V., Richards, S. M., Bevan, A. P., Clayton, S., Corpas, M., Rajan, D., Vooren, S. V., Moreau, Y., Pettett, R. M., & Carter, N. P. (2009). DECIPHER: Database of Chromosomal Imbalance and Phenotype in Humans Using Ensembl Resources. *American Journal of Human Genetics* , *84* (4), 524–533. https://doi.org/10.1016/j.ajhg.2009.03.010

Fountain, M. D., Oleson, D. S., Rech, M. E., Segebrecht, L., Hunter, J. V., McCarthy, J. M., Lupo, P. J., Holtgrewe, M., Moran, R., Rosenfeld, J. A., Isidor, B., Le Caignec, C., Saenz, M. S., Pedersen, R. C., Morgan, T. M., Pfotenhauer, J. P., Xia, F., Bi, W., Kang, S.-H. L., ... Schaaf, C. P. (2019). Pathogenic variants in USP7 cause a neurodevelopmental disorder with speech delays, altered behavior, and neurologic anomalies. *Genetics in Medicine* , *21* (8), 1797–1807. https://doi.org/10.1038/s41436-019-0433-1

French, C. E., Delon, I., Dolling, H., Sanchis-Juan, A., Shamardina, O., Mégy, K., Abbs, S., Austin, T., Bowdin, S., Branco, R. G., Firth, H., NIHR BioResource—Rare Disease, Next Generation Children Project, Rowitch, D. H., & Raymond, F. L. (2019). Whole genome sequencing reveals that genetic conditions are frequent in intensively ill children. *Intensive Care Medicine* , *45* (5), 627–636. https://doi.org/10.1007/s00134-019-05552-x

Hao, Y.-H., Fountain, M. D., Fon Tacer, K., Xia, F., Bi, W., Kang, S.-H. L., Patel, A., Rosenfeld, J. A., Le Caignec, C., Isidor, B., Krantz, I. D., Noon, S. E., Pfotenhauer, J. P., Morgan, T. M., Moran, R., Pedersen, R. C., Saenz, M. S., Schaaf, C. P., & Potts, P. R. (2015). USP7 Acts as a Molecular Rheostat to Promote WASH-Dependent Endosomal Protein Recycling and Is Mutated in a Human Neurodevelopmental Disorder.*Molecular Cell* , *59* (6), 956–969. https://doi.org/10.1016/j.molcel.2015.07.033

Karczewski, K. J., Francioli, L. C., Tiao, G., Cummings, B. B., Alföldi, J., Wang, Q., Collins, R. L., Laricchia, K. M., Ganna, A., Birnbaum, D. P., Gauthier, L. D., Brand, H., Solomonson, M., Watts, N. A., Rhodes, D., Singer-Berk, M., England, E. M., Seaby, E. G., Kosmicki, J. A., ... MacArthur, D. G. (2020). The mutational constraint spectrum quantified from variation in 141,456 humans. *Nature* ,*581* (7809), 434–443. https://doi.org/10.1038/s41586-020-2308-7

Landrum, M. J., Lee, J. M., Benson, M., Brown, G. R., Chao, C., Chitipiralla, S., Gu, B., Hart, J., Hoffman, D., Jang, W., Karapetyan, K., Katz, K., Liu, C., Maddipatla, Z., Malheiro, A., McDaniel, K., Ovetsky, M., Riley, G., Zhou, G., ... Maglott, D. R. (2018). ClinVar: Improving access to variant interpretations and supporting evidence. *Nucleic Acids Research* , *46* (Database issue), D1062–D1067. https://doi.org/10.1093/nar/gkx1153

Lionel, A. C., Costain, G., Monfared, N., Walker, S., Reuter, M. S., Hosseini, S. M., Thiruvahindrapuram, B., Merico, D., Jobling, R., Nalpathamkalam, T., Pellecchia, G., Sung, W. W. L., Wang, Z., Bikangaga, P., Boelman, C., Carter, M. T., Cordeiro, D., Cytrynbaum, C., Dell, S. D., ... Marshall, C. R. (2018). Improved

diagnostic yield compared with targeted gene sequencing panels suggests a role for whole-genome sequencing as a first-tier genetic test. *Genetics in Medicine* ,*20* (4), 435–443. https://doi.org/10.1038/gim.2017.119

Malhotra, A., Ziegler, A., Shu, L., Perrier, R., Amlie-Wolf, L., Wohler, E., Lygia de Macena Sobreira, N., Colin, E., Vanderver, A., Sherbini, O., Stouffs, K., Scalais, E., Serretti, A., Barth, M., Navet, B., Rollier, P., Xi, H., Wang, H., Zhang, H., ... Bonneau, D. (2021). De novo missense variants in LMBRD2 are associated with developmental and motor delays, brain structure abnormalities and dysmorphic features.*Journal of Medical Genetics* , *58* (10), 712–716. https://doi.org/10.1136/jmedgenet-2020-107137

Moysés-Oliveira, M., Giannuzzi, G., Fish, R. J., Rosenfeld, J. A., Petit, F., Soares, M. de F., Kulikowski, L. D., Di-Battista, A., Zamariolli, M., Xia, F., Liehr, T., Kosyakova, N., Carvalheira, G., Parker, M., Seaby, E. G., Ennis, S., Gilbert, R. D., Hagelstrom, R. T., Cremona, M. L., ... Reymond, A. (2018). Inactivation of*AMMECR1* is associated with growth, bone, and heart alterations.*Human Mutation* , *39* (2), 281–291. https://doi.org/10.1002/humu.23373

NICUSeq Study Group, Krantz, I. D., Medne, L., Weatherly, J. M., Wild, K. T., Biswas, S., Devkota, B., Hartman, T., Brunelli, L., Fishler, K. P., Abdul-Rahman, O., Euteneuer, J. C., Hoover, D., Dimmock, D., Cleary, J., Farnaes, L., Knight, J., Schwarz, A. J., Vargas-Shiraishi, O. M., ... Taft, R. J. (2021). Effect of Whole-Genome Sequencing on the Clinical Management of Acutely Ill Infants With Suspected Genetic Disease: A Randomized Clinical Trial. *JAMA Pediatrics* . https://doi.org/10.1001/jamapediatrics.2021.3496

Okur, V., Watschinger, K., Niyazov, D., McCarrier, J., Basel, D., Hermann, M., Werner, E. R., & Chung, W. K. (2019). Biallelic variants in AGMO with diminished enzyme activity are associated with a neurodevelopmental disorder. *Human Genetics* , *138* (11–12), 1259–1266. https://doi.org/10.1007/s00439-019-02065-x

Radio, F. C., Pang, K., Ciolfi, A., Levy, M. A., Hernández-García, A., Pedace, L., Pantaleoni, F., Liu, Z., de Boer, E., Jackson, A., Bruselles, A., McConkey, H., Stellacci, E., Lo Cicero, S., Motta, M., Carrozzo, R., Dentici, M. L., McWalter, K., Desai, M., ... Tartaglia, M. (2021). SPEN haploinsufficiency causes a neurodevelopmental disorder overlapping proximal 1p36 deletion syndrome with an episignature of X chromosomes in females. *The American Journal of Human Genetics* , *108* (3), 502–516. https://doi.org/10.1016/j.ajhg.2021.01.015

Scocchia, A., Wigby, K. M., Masser-Frye, D., Del Campo, M., Galarreta, C. I., Thorpe, E., McEachern, J., Robinson, K., Gross, A., Ajay, S. S., Rajan, V., Perry, D. L., Belmont, J. W., Bentley, D. R., Jones, M. C., & Taft, R. J. (2019). Clinical whole genome sequencing as a first-tier test at a resource-limited dysmorphology clinic in Mexico. *NPJ Genomic Medicine* , *4* , 5. https://doi.org/10.1038/s41525-018-0076-1

Sobreira, N., Schiettecatte, F., Valle, D., & Hamosh, A. (2015). GeneMatcher: A Matching Tool for Connecting Investigators with an Interest in the Same Gene. *Human Mutation* , *36* (10), 928–930. https://doi.org/10.1002/humu.22844

Strande, N. T., Riggs, E. R., Buchanan, A. H., Ceyhan-Birsoy, O., DiStefano, M., Dwight, S. S., Goldstein, J., Ghosh, R., Seifert, B. A., Sneddon, T. P., Wright, M. W., Milko, L. V., Cherry, J. M., Giovanni, M. A., Murray, M. F., O'Daniel, J. M., Ramos, E. M., Santani, A. B., Scott, A. F., ... Berg, J. S. (2017). Evaluating the Clinical Validity of Gene-Disease Associations: An Evidence-Based Framework Developed by the Clinical Genome Resource. *American Journal of Human Genetics* ,*100* (6), 895–906. https://doi.org/10.1016/j.ajhg.2017.04.015

Sun, J.-H., Chen, J., Ayala Valenzuela, F. E., Brown, C., Masser-Frye, D., Jones, M., Romero, L. P., Rinaldi, B., Li, W. L., Li, Q.-Q., Wu, D., Gerard, B., Thorpe, E., Bayat, A., & Shi, Y. S. (2021). X-linked neonatal-onset epileptic encephalopathy associated with a gain-of-function variant p.R660T in GRIA3. *PLoS Genetics* ,*17* (6), e1009608. https://doi.org/10.1371/journal.pgen.1009608

Turro, E., Astle, W. J., Megy, K., Gräf, S., Greene, D., Shamardina, O., Allen, H. L., Sanchis-Juan, A., Frontini, M., Thys, C., Stephens, J., Mapeta, R., Burren, O. S., Downes, K., Haimel, M., Tuna, S., Deevi, S. V. V., Aitman, T. J., Bennett, D. L., ... Ouwehand, W. H. (2020). Whole-genome sequencing of patients

with rare diseases in a national health system. *Nature* , *583* (7814), 96–102. https://doi.org/10.1038/s41586-020-2434-2

Vanderver, A., Bernard, G., Helman, G., Sherbini, O., Boeck, R., Cohn, J., Collins, A., Demarest, S., Dobbins, K., Emrick, L., Fraser, J. L., Masser-Frye, D., Hayward, J., Karmarkar, S., Keller, S., Mirrop, S., Mitchell, W., Pathak, S., Sherr, E., … Taft, R. J. (2020). Randomized Clinical Trial of First-Line Genome Sequencing in Pediatric White Matter Disorders. *Annals of Neurology* , *88* (2), 264–273. https://doi.org/10.1002/ana.25757

Zech, M., Bardakjian, T. M., Stoklosa, M., Ploski, R., Jech, R., Gonzalez-Alegre, P., & Winkelmann, J. (2021). A Neurodevelopmental Disorder With Dystonia and Chorea Resulting From Clustering *CAMK4* Variants. *Movement Disorders* , *36* (2), 520–521. https://doi.org/10.1002/mds.28398

Table 1. Summary of submissions to GeneMatcher (submitted as a separate file)

Table 2. Summary of publications arising from GeneMatcher collaborations to date (submitted as a separate file).

Figure legends

Figure 1: Minimum criteria for candidate genes for submission to GeneMatcher.

Figure 2: Workflow for submission of candidate genes to GeneMatcher.

Hosted file

`Table 1. Summary of submissions to GeneMatcher.docx` available at https://authorea.com/users/440346/articles/541117-a-clinical-laboratory-s-experience-using-genematcher-building-stronger-gene-disease-relationships

Hosted file

`Table 2. Summary of publications arising from GeneMatcher collaborations to date.docx` available at https://authorea.com/users/440346/articles/541117-a-clinical-laboratory-s-experience-using-genematcher-building-stronger-gene-disease-relationships

Hosted file

`Figure_1.docx` available at https://authorea.com/users/440346/articles/541117-a-clinical-laboratory-s-experience-using-genematcher-building-stronger-gene-disease-relationships