

Discussion

The Interdisciplinary Diagnosis of Rare Diseases

Results of the Translate-NAMSE Project

by Dr. med. Franziska Rillig, Prof. Dr. med. Annette Grüters, Prof. Dr. med. Tobias Bäumer, et al. in issue 27–28/2022

Similar Results in Human Geneticists' Practices

The results of the prospective study (1) are mostly consistent with my results obtained over the same time period in our statutory health insurance physician's practice: since the fourth quarter of 2017, I referred from a total of 4400 treatment contacts 385 to mendeliome or exome analysis (2398—19 433 genes)—without a case conference. Confirmation of genetic variants of pathogenic classes 4 or 5 (2) yielded a rate of 107 diagnoses (28%); 32% in n = 145 ≤18-year-olds and 25% in n = 240 >18-year-olds. Most of the diagnoses—almost without exception from the groups of ultra-rare and rare diseases—were identified only once. Few of the diagnoses were identified more than once. In addition to my own clinical-genetic findings, I have available for my consultations the telephone, prior findings from social pediatric centers (*Sozialpädiatrische Zentren, SPZ*), specialist ambulances, hospitals, and statutory health insurance physicians' practices. The spectacular diagnosis rates in the classic-genetic proportion of rare diseases (75–80%) are based primarily on the relatively new technique of exome analysis. This technology is available to all 136 German practices and outpatient clinics offering genetic consultations (3, 4). The rightly criticized (1) diagnostic odyssey could in my opinion be avoided by timely referral to a genetic consultation. We can assume that the 14 850 (sic!) case conferences (1) in the 10 participating centers consumed substantial resources, despite which 70% of

cases remained undiagnosed (1). It would be wrong and uneconomical to perpetuate such an approach in statutory health care funded by members' contributions. Multidisciplinary case conferences in genome sequencing have now even become required by law (§ 64e SGB [social code] V). The data cited in (1) collected internationally and from German statutory health insurance practices (4) show that the same diagnostic success rate as in (1) can be achieved entirely without case conferences. The obvious suggestion is that human genetic consultations be offered close to people's residences and as a step before accessing the centers for rare diseases. DOI: 10.3238/arztebl.m2022.0351

References

1. Rillig F, Grüters A, Bäumer T, et al.: The interdisciplinary diagnosis of rare diseases—results of the Translate-NAMSE project. *Dtsch Arztebl Int* 2022; 119: 469–75.
2. Richards S, Aziz N, Bale S, et al.: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 2015; 17: 405–24.
3. Berufsverband Deutscher Humangenetiker BVdH e.V.: www.bvdh.de/public.php?id=5 (last accessed on 10 October 2022).
4. Neuhann TM, Schulte B, Lüdeke M, et al.: Exomdiagnostik bei Kindern mit Entwicklungsverzögerung—Erfahrungen aus Diagnostikzentren in Deutschland. *Neuropädiatrie* 2022; 17: 76–85.

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In Reply:

Dr Finkh's comments support the importance of exome analysis in diagnosis rare diseases, which often have genetic causes. We wish to emphasize, however, that in the Translate-NAMSE Project, exome analysis is integrated in an interdisciplinary treatment concept at centers for rare diseases, with participation of different medical specialties, including obligatory participation of human genetics. The specialties are involved on a patient-specific basis and include the laborious work-up of the patients' medical results as well as recommendations for continued care after a diagnosis has been made and therapeutic recommendations and access to clinical treatment studies (national and often international).

A total of 5652 persons with unknown diseases received healthcare in the study, a diagnosis was possible in 1682, and exome analysis enabled a diagnosis in 506 of these. We showed that interdisciplinary case conferences are not only crucial for defining a targeted indication for exome analysis—and therefore also contribute to avoiding unnecessary exome analysis—but are also able in a large number of patients (n=1176) to make an often non-genetic diagnosis from all medical specialties.

We are convinced that if care is not based on interdisciplinary case conferences the patients' odyssey will continue, owing to the genetic variants that can often be interpreted in a clinically unequivocal way only with a great deal of effort, and because of the difficulty in finding specific treatment expertise. This will even be exacerbated by the diagnostic sequencing of the entire genome (for which the German legislature has created the prerequisites with the model project according to §64e). The information contained in the non-coding regions of the genome is far more difficult to interpret, and interdisciplinary expertise will be even more crucial in this setting. DOI: 10.3238/arztebl.m2022.0352

References

1. Rillig F, Grüters A, Bäumer T, et al.: The interdisciplinary diagnosis of rare diseases—results of the Translate-NAMSE project. *Dtsch Arztebl Int* 2022; 119: 469–75.

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Conflict of interest statement

The authors of both contributions declare that no conflict of interest exists.