

COMMENTARY TO HABILITATION THESIS¹

Despite their individually low prevalence, rare diseases represent a major health and societal challenge. In the European Union, they are defined as life-threatening or serious chronic conditions with a prevalence of fewer than 5 in 10,000 people; the United States (Orphan Drug Act, 1983) and Japan use similar definitions with different numerical thresholds. Collectively, rare diseases affect approximately 1 in 16 Europeans, corresponding to 27–36 million people, and hundreds of millions worldwide. Approximately 80% of rare diseases have a genetic basis, around 70% manifest during childhood, and up to 30% of affected children do not survive beyond the age of five [1].

Their diagnosis is complicated by the extraordinary heterogeneity of clinical presentations, limited access to specialized expertise and, in some patients, a molecular or nosological basis that has yet to be identified. The resulting diagnostic odyssey lasts an average of 4.7–5 years according to EURORDIS data, exceeds five years in one quarter of patients, and includes at least one misdiagnosis in one half to three quarters of affected individuals [1]. Rather than merely describing the available methods and approaches, this habilitation thesis synthesises the results of a program that we have been developing at University Hospital Brno (UHB) since 2019, encompassing the entire pathway from clinical indication and genomic analysis through functional validation of variants to the therapeutic and systemic application of diagnostic findings.

The program originated from an evaluation of the utility of singleton WES in a pilot cohort of undiagnosed pediatric patients at UHB. The results [2] demonstrated a diagnostic yield comparable to that of international programs and confirmed the feasibility of a multidisciplinary organizational model for undiagnosed pediatric patients at UHB. The results further provided the basis for establishing the Multidisciplinary Indication Committee, the first dedicated Outpatient Clinic for Undiagnosed Pediatric Patients in the Czech Republic in 2023, and the UHB Undiagnosed Patients (UDP) Program. In a cohort of 58 patients, 28 relevant variants were identified in 25 children (43%), with the clinical utility of the findings reaching 76%. Subsequent publications broadened the phenotypic spectrum associated with the causative genes *PMM2* [3], *MYRF* [4] and *DYRK1A* [5] and described the first Czech cases of disorders associated with *PPP2R5D* [6] and ReNU syndrome [7]. The rapid identification of ReNU syndrome also demonstrated the importance of continuous genomic data reanalysis. To date, a total of 387 patients have been enrolled in the UHB UDP Program, with a diagnostic yield of 38%.

A further dimension is the integration of the clinical program with functional genomics and translational precision medicine at the CREATIC. This integrated coordination platform enables clinical characterization to guide the direction of laboratory research and its results to be translated back into the care of the individual patient. Functional analyses of *CYP2U1* variants combining molecular structural modelling, cellular model systems and enzymatic assays clarified their pathogenicity, supported their reclassification and opened the possibility of exploring experimental gene therapy [8]. A similar integrative approach was applied to a variant in the *ADAR* gene [9]. The developing platform also includes individualized drug

¹ The commentary must correspond to standard expectations in the field and must include a brief characteristic of the investigated matter, objectives of the work, employed methodologies, obtained results and, in case of co-authored works, a passage characterising the applicant's contribution in terms of both quality and content.

repurposing focused not on the disease in general, but on the specific gene and variant identified in the individual patient.

Experience gained through the UDP program enabled the establishment of Baby Fox, the first nationwide rapid whole-genome sequencing program for critically ill neonates and children in the Czech Republic, which is coordinated both clinically and at the laboratory level from UHB. By August 2026, the program had enrolled 89 patients and achieved a diagnostic yield of 43.8%, a clinically relevant result in 57.3%, and a mean turnaround time of five days from sample collection to report issuance. In 60% of diagnosed patients, the finding had a direct impact on clinical care.

The significance of the UDP program extends beyond individual publications and projects and is also reflected in the organization of the healthcare system. Experience gained during its development informed the preparation of the National Strategy for Rare Diseases 2026–2035, whose SWOT analysis identifies the UHB UDP program as one of the strengths of the system. The program therefore demonstrates how a clinically embedded model can effectively integrate genomic diagnostics, specialized care and translational research while contributing to the further development of care for patients with rare and undiagnosed diseases at the national level.

[1]² SLABÁ, Kateřina, Petra POKORNÁ, Kamila ŘÍHOVÁ, Regina DEMLOVÁ a Ondřej SLABÝ. Výzvy a perspektivy diagnostiky dětských pacientů bez diagnózy a přehled léčebných možností u vzácných onemocnění. *Neurol. praxi*. 2026;**27**(2):89-95. ISSN 1213-1814. Dostupné z: doi: [10.36290/neu.2026.017](https://doi.org/10.36290/neu.2026.017)

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
0	100	80	100

[2] SLABA, Katerina *(corresponding author)*, Petra POKORNA, Robin JUGAS, Hana PALOVA, Dagmar PROCHAZKOVA, Stefania AULICKA, Klara SPANELOVA, Pavlina DANHOFFER, Ondrej HORAK, Jana TUCKOVA, Petra KLEIBLOVA, Renata GAILLYOVA, Matej HRUNKA, Martin JOUZA, Blanka PINKOVA, Jan PAPEZ, Petra KONECNA, Jana ZIDKOVA, Petr STOURAC, Jaroslav STERBA, Regina DEMLOVA, Eva DEMLOVA, Petr JABANDZIEV and Ondrej SLABY. Diagnostic efficacy and clinical utility of whole-exome sequencing in Czech pediatric patients with rare and undiagnosed diseases. *Scientific Reports* [online]. 2024, **14**(1, Article 28780). ISSN 2045-2322. Available at: doi:10.1038/s41598-024-79872-4

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
50	70	80	70

[3] SLABA, Katerina, Hana NOSKOVA, Petra VESELA, Jana TUCKOVA, Hana JICINSKA, Tomas HONZIK, Hana HANSIKOVA, Petra KLEIBLOVA, Petr STOURAC, Petr JABANDZIEV, Ondrej SLABY and Dagmar PROCHAZKOVA. Novel Splicing Variant in the PMM2 Gene in a Patient With PMM2-CDG Syndrome Presenting With Pericardial Effusion: A Case Report. *Frontiers In Genetics* [online]. 2020, **11**(561054, Article 561054). ISSN 1664-8021. Available at: doi:10.3389/fgene.2020.561054

² Bibliographic record of a published scientific result, which is part of the habilitation thesis.

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
50	50	80	70

[4] SLABA, Katerina, Marta JEZOVA, Petra POKORNA, Hana PALOVA, Jana TUCKOVA, Jan PAPEZ, Dagmar PROCHAZKOVA, Petr JABANDZIEV and Ondrej SLABY. Two sisters with cardiac-urogenital syndrome secondary to pathogenic splicing variant in the MYRF gene with unaffected parents: A case of gonadal mosaicism?. *Molecular Genetics & Genomic Medicine* [online]. 2023, **11**(5). ISSN 2324-9269. Available at: doi:10.1002/mgg3.2139

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
50	50	80	70

[5] SLABÁ, Kateřina, Hana PÁLOVÁ, Petra POKORNÁ, Ondřej SLABÝ, Petra KONEČNÁ, Lucie KOLBOVÁ, Petr JABANDŽIEV and Dagmar PROCHÁZKOVÁ. DYRK1A-related intellectual disability syndrome; [Syndrom intelektuálního postižení související s DYRK1A]. *Cesko-Slovenska Pediatrie* [online]. 2022, **77**(4), 215–218. ISSN 0069-2328. Available at: doi:10.55095/CSPediatric2022/035

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
50	50	80	70

[6] SLABA, K., H. PALOVA, P. VESELA, S. AULICKA, P. KONECNA, M. STERBA, P. JABANDZIEV, O. SLABY and D. PROCHAZKOVA. PPP2R5D-related intellectual disability and neurodevelopmental delay - the first case in the Czech Republic. *Ceska A Slovenska Neurologie A Neurochirurgie* [online]. 2021, **84**(2), 205–207. ISSN 1802-4041. Available at: doi:10.48095/cccsnn2021205

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
50	50	90	80

[7] SLABÁ, Kateřina, Petra POKORNÁ, Kateřina KOŽELKOVÁ, Eliška HLOUŠKOVÁ, Robin JUGAS, Jana KUBÁTOVÁ, Regina DEMLOVÁ, Pavlína DANHOFER, Petr JABANDŽIEV, Tereza SVATOŇOVÁ and Ondřej SLABÝ. ReNU syndrome – a newly described prevalent neurodevelopmental disorder: first case in the Czech Republic; [ReNU syndrom – nově popsané prevalentní neurovývojové onemocnění, první případ v České republice]. *Cesko-Slovenska Pediatrie* [online]. 2025, **80**(4), 177–181. ISSN 0069-2328. Available at: doi:10.55095/CSPediatric2025/029

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
50	50	100	90

[8] SUSTROVA, Eva, Kamila RIHOVA, Petra POKORNA, Veronika HAVLOVA, Marek STIBOREK, Zdenek SIMEK, Jiri DAMBORSKY, Ondrej HORAK, Katerina KOZELKOVA, Eliska HLOUSKOVA, Regina DEMLOVA, Jana KUBATOVA, Ondrej SLABY and **Katerina SLABA *(corresponding author)***. Early-onset hereditary spastic paraplegia type 56 (SPG56): clinical-molecular correlations and functional validation of CYP2U1 variants. *BMC*

Medical Genomics [online]. 2026, **19**(1, Article 117). ISSN 1755-8794. Available at: doi:10.1186/s12920-026-02394-7

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
50	90	70	70

[9] TURAN, Katerina, Petra POKORNA, Kamila RIHOVA, Jana KUBATOVA, Katerina KOZELKOVA, Eliska HLOUSKOVA, Pavlina DANHOFER, Petr JABANDZIEV, Jiri DAMBORSKY, Regina DEMLOVA, Ondrej SLABY and **Katerina SLABA** **(corresponding author)**. Aicardi-Goutieres Syndrome Type 6: Case Report and Structural Prediction Supporting a Dominant-Negative Effect of the ADAR1 c.3019G>A Variant. *Clinical Case Reports* [online]. 2026, **14**(4, Article e72146). ISSN 2050-0904. Available at: doi:10.1002/ccr3.72146

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
50	90	70	70