


LETTER TO THE EDITOR

Open Access



# Rare diseases' genetic newborn screening as the gateway to future genomic medicine: the Screen4Care EU-IMI project

Alessandra Ferlini<sup>1\*</sup> , Edith Sky Gross<sup>2</sup>, Nicolas Garnier<sup>3</sup> and on behalf of the Screen4Care consortium

## Abstract

Following the reverse genetics strategy developed in the 1980s to pioneer the identification of disease genes, genome(s) sequencing has opened the era of genomics medicine. The human genome project has led to an innumerable series of applications of omics sciences on global health, from which rare diseases (RDs) have greatly benefited. This has propelled the scientific community towards major breakthroughs in disease genes discovery, in technical innovations in bioinformatics, and in the development of patients' data registries and omics repositories where sequencing data are stored. Rare diseases were the first diseases where nucleic acid-based therapies have been applied. Gene therapy, molecular therapy using RNA constructs, and medicines modulating transcription or translation mechanisms have been developed for RD patients and started a new era of medical science breakthroughs. These achievements together with optimization of highly scalable next generation sequencing strategies now allow movement towards genetic newborn screening. Its applications in human health will be challenging, while expected to positively impact the RD diagnostic journey. Genetic newborn screening brings many complexities to be solved, technical, strategic, ethical, and legal, which the RD community is committed to address. Genetic newborn screening initiatives are therefore blossoming worldwide, and the EU-IMI framework has funded the project Screen4Care. This large Consortium will apply a dual genetic and digital strategy to design a comprehensive genetic newborn screening framework to be possibly translated into the future health care.

**Keywords** Rare diseases, Genetic newborn screening, Next generation sequencing, Digital health, European Union

## The path toward genomic medicine

The human genome project, via an innumerable series of applications of omics sciences on global health, has led important implications in rare diseases (RDs) [1]. Among these, the Online Mendelian Inheritance in Man (OMIM, <https://omim.org>), is now a free repository which lists all

known mendelian genes in which pathogenic variations cause RDs [2]. Besides, several RD registries and datasets are available worldwide providing huge data sets of patient's phenotypes and genotypes [3, 4].

This RD intensive research, accompanied by the development of new therapies, prompts for updated newborn screening strategies, to gain early diagnosis by population screening in all neonates in a defined geography. Since the first Guthrie test for phenylketonuria (PKU) in 1961, biochemical NBS for many treatable RDs have become available, although differently adopted by health systems in various countries across the world [5]. Biochemical tests were further implemented by tandem mass spectrometry (MS/MS) and are currently performed on

\*Correspondence:

Alessandra Ferlini  
fla@unife.it

<sup>1</sup> Medical Genetics Unit, Department of Medical Sciences, University of Ferrara, 44121 Ferrara, Italy

<sup>2</sup> EURORDIS – Rare Diseases Europe, Paris, France

<sup>3</sup> Pfizer Inc., Collegetown 19426 PA, USA



© The Author(s) 2023. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

screening blood spot cards. Metabolic screening had an immense impact on patients by early detection at a relatively low cost and revolutionized the natural history of many RD types. Nevertheless, significant limitations remain. First, metabolic NBS can be adopted only for diseases which have disease-specific analytes; second, it explores phenotypes, implying that genetic diagnosis must be subsequently very often carried out for disease confirmation; and third, conflicting results are not infrequent [6]. Consequently, only a limited number of RDs are currently identifiable by metabolic NBS and can benefit from this extraordinary screening tool. Several initiatives are ongoing to explore the feasibility of genetic NBS (gNBS) on a large-scale, using different next-generation sequencing (NGS) approaches [7–12]. The international Consortium (ICoNS, <https://www.iconseq.org>) was thoughtfully established to enhance collaboration and data sharing among these initiatives.

Broad implementation of gNBS holds tremendous promise, but also raises important ethical questions. As in routine genetic diagnosis, gNBS needs to meet quality standards, such as accuracy (identifying the variant correctly), sensitivity (probability to detect the variations), specificity (ability to not identify the variations in non-carriers) and clinical validity (ability to predict a specific phenotype) [13].

Different techniques could be adopted, including targeted sequencing (or TS, also defined as ‘on demand’ gene panels), whole exome sequencing (WES), or whole genome sequencing (WGS). While TS is validated and widely used in diagnostics, WGS might start to gradually replace TS, as soon as WGS can fulfil the standards mentioned above, in addition to possibly becoming more cost effective than TS [14–16].

gNBS must be able to identify all mutation types, including copy number variations (CNVs), to confer full accuracy to the testing; robust data pipelines for variants’ calling prioritization and validation are needed, and gNBS for not deferrable RDs (eligible for interventions or therapy in a certain, not flexible, temporal window) needs appropriate reporting turnaround time. All these issues encourage the use of large and high-throughput platforms able to process thousands of samples to secure timely access to care.

Irrespective of the techniques we may prefer to adopt for gNBS, selecting genes/diseases to be screened and how and to whom reports shall be communicated is a crucial task. Following the EURORDIS document listing the 11 key principles to be considered for NBS (<https://www.eurordis.org/publications/key-principles-for-newborn-screening>), we need to “decrypt” the definitions of treatable and actionable conditions, before finding rigorous rules for their inclusion in gNBS. The

next critical step is reaching some level of consensus on how to build robust genes/diseases selection criteria. An arbitrary disease selection based on technique popularity or availability, or on subjective preference from any stakeholder, not evidenced based, will be unsuccessful. In addition, the RD advocacy community will need to provide evidence that proposed gNBS programs meet the needs of patients. It will be crucial finding a consensus about minimal requirements needed for gNBS adoption in health systems, depending on geographies, cultures, preferences, and means. Related to this last point, the large genetic datasets generated in diverse ethnicities will provide unique information about population-specific clinical utility of gNBS for certain diseases, fact that will possibly address the more appropriate methods to be used. Finally, if gNBS will be adopted by health systems, an unprecedented amount of data will be generated, raising outstanding issues related to data privacy, ethics, and ownership, and how to make optimal and appropriate use of them both in research and healthcare contexts [17].

### **Screen4Care: an EU-IMI funded project for RDs early diagnosis**

The European Commission (EC), through its Innovative Medicines Initiative (IMI) has funded the research project Screen4Care ([www.screen4care.eu](http://www.screen4care.eu)). This five-year long project, launched in October 2021, is based on a “private public patient partnership” or “PPPP” including 36 partners working together in a coordinated way to define, develop, and pilot the “optimal” comprehensive framework for gNBS to be proposed as part of a future healthcare. The EC has dedicated an impressive amount of funding into RD research, with an established and successful track record of delivering results. It is therefore not at all surprising that EC has deemed it important to invest in such a project oriented towards genetic newborn screening and digital health. Indeed, Screen4Care (S4C) will use a multi-pronged strategy to shorten the time to diagnosis for RD patients. Firstly, it is undertaking an ecosystem systematic scoping of all significant initiatives on RDs’ diagnosis and genetic NBS in Europe. This will establish a S4C RD federated meta data platform. A second pillar of the project is running a “real life” gNBS in about 25,000 infants in Europe, the largest population ever genetically screened before [18], using custom, “ad hoc” designed, gene panels. Disease prioritization will be conceptualized around treatable diseases, after having defined what “treatable” means. This will be achieved by delineating a robust scoring method which will be used to identify “treatable” diseases and then applied on a broader yet specific actionable disease spectrum, this last enriched by insights from a large public survey conducted by EURORDIS. The S4C gNBS work

package also includes design of gNBS pipeline(s) adapted to the participating countries, from preference studies to technical setting, ethical considerations, also using telegenetics and telemedicine. Among the 25,000 screened infants, those manifesting early symptoms of a RD (any) within a 1–2 year follow up, though resulted negative at the genetic panel screening, will receive whole genome sequencing WGS. In addition, S4C will develop several digital tools based on Artificial Intelligence-trained algorithms to identify phenotypes in patients at early disease onset and to help them in their diagnosis journey. S4C pillars will be complemented by cost/benefit evaluation, enabling S4C to put forth technically, ethically, and economically sustainable gNBS framework.

S4C is rooted in sharing and dialoguing, especially with the NBS community to harmonize metabolic and genetic NBS approaches, to contribute to a larger consensus on the most effective NBS-gNBS strategies and other early diagnosis models, adaptable to context-specific environments and health systems. We underline that the involvement in the S4C of the RD community with the active role of EURORDIS as a full partner, represents an added value since it will allow to define views and perceptions of society about gNBS, as already recommended worldwide [19].

We believe, as it happened in the Human Genome project, that defining gNBS appropriate path(s) for RDs will benefit both health system and genomic medicine future avenues, representing a pioneering global health approach.

#### Abbreviations

RD	Rare disease
gNBS	Genetic newborn screening
S4C	Screen4Care
WGS	Whole genome sequencing
WES	Whole exome sequencing
TS	Targeted sequencing
CNV	Copy number variation

#### Acknowledgements

We acknowledge all the S4C partnership which is visible at the S4C website. \*Screen4Care Consortium members. Joanne Berghout, Pfizer Inc., Collegeville, 19426 PA, USA. Aldona Zygmunt, Pfizer Inc., Collegeville, 19426 PA, USA. Deependra Singh, Pfizer Inc., Collegeville, 19426 PA, USA. Kui A. Huang, Pfizer Inc., Collegeville, 19426 PA, USA. Waltraud Kantz, Pfizer Inc., Collegeville, 19426 PA, USA. Carl Rudolf Blankart, KPM Center for Public Management and Swiss Institute for Translational and Entrepreneurial Medicine, University of Bern, Switzerland. Sandra Gillner, KPM Center for Public Management and Swiss Institute for Translational and Entrepreneurial Medicine, University of Bern, Switzerland. Jiawei Zhao, Department for Mathematics and Computer Science, University of Southern Denmark, Denmark. Richard Roettger Department for Mathematics and Computer Science, University of Southern Denmark, Denmark. Christina Saier, Department of Neuropediatrics and Muscle Disorders, Medical Center, University of Freiburg, Germany. Jan Kirschner Department of Neuropediatrics and Muscle Disorders, Medical Center, University of Freiburg, Germany. Joern Schenk, Takeda Pharmaceuticals International AG, Switzerland. Leon Atkins, Takeda Pharmaceuticals International AG, Switzerland. Nuala Ryan, Takeda Pharmaceuticals International AG, Switzerland. Kaja

Zarakowska, Takeda Pharmaceuticals International AG, Switzerland. Jana Zschüntzsch, Universitaetsmedizin Goettingen—Georg-August-Universitaet Goettingen—Stiftung Oeffentlichen Rechts, Germany. Michela Zuccolo, F. Hoffmann La-Roche, Grenzacherstrasse 124, 4070 Basel, Switzerland. Matthias Müllenborn, Novo Nordisk Health Care AG, Switzerland. Yuen-Sum Man, Novo Nordisk Health Care AG, Switzerland. Liz Goodman, University College Dublin, National University of Ireland, Ireland. Marie Trad Lysogene, Neuilly-sur-Seine, France. Anne Sophie Chalandon, Sanofi, Diegem, Belgium. Stefan Sansen, Sanofi, Diegem, Belgium. Maria Martinez-Fresno, Illumina, UK Shirlene Badger, Illumina, UK. Rudolf Walther van Olden, Novartis Gene Therapies Switzerland GmbH. Robert Rothmann, Ludwig Boltzmann Gesellschaft GmbH Research Institute AG & Co KG, Digital Human Rights Center, Wollzeile 1/1/, Wien. Patrick Lehner, Ludwig Boltzmann Gesellschaft GmbH Research Institute AG & Co KG, Digital Human Rights Center, Wollzeile 1/1/, Wien. Christof Tsocholi, Ludwig Boltzmann Gesellschaft GmbH Research Institute AG & Co KG, Digital Human Rights Center, Wollzeile 1/1/, Wien. Ludovic Baillon, PTC Therapeutics Switzerland GmbH, 6312 Steinhausen Schweiz. Gulcin Gumus, EURORDIS, France. Rumen Stefanov, Department of Social Medicine and Public Health, Faculty of Public Health, Medical University of Plovdiv, Plovdiv, Bulgaria. Georgi Iskrov, Department of Social Medicine and Public Health, Faculty of Public Health, Medical University of Plovdiv, Plovdiv, Bulgaria. Ralitsa Raycheva, Department of Social Medicine and Public Health, Faculty of Public Health, Medical University of Plovdiv, Plovdiv, Bulgaria. Kostadin Kostadinov, Department of Social Medicine and Public Health, Faculty of Public Health, Medical University of Plovdiv, Plovdiv, Bulgaria. Bulgari Georgi Stefanov, Department of Social Medicine and Public Health, Faculty of Public Health, Medical University of Plovdiv, Plovdiv, Bulgaria. Elena Mitova, Department of Social Medicine and Public Health, Faculty of Public Health, Medical University of Plovdiv, Plovdiv, Bulgaria. Moshe Einhorn, Genoox (Tel Aviv, Israel). Yaron Einhorn, Genoox (Tel Aviv, Israel). Josef Schepers, Charité – Universitätsmedizin Berlin, Berlin Institute of Health. Miriam Hübner, Charité – Universitätsmedizin Berlin, Berlin Institute of Health. Frauke Alves, Translational Molecular Imaging, Max Planck Institute for Multidisciplinary Sciences, Göttingen, Germany. Rowan Iskandar, Center of Excellence in Decision-Analytic Modeling and Health Economics Research (sitem-insel) AG, Bern, Switzerland. Rudolf Mayer, SBA Research gGmbH, Wien, Austria. Alessandra Renieri, Medical Genetics, University of Siena, Italy. Aneta Piperkova, Personalized Medicine; Digital Health; Patient Advocate, Bulgaria. Ivo Gut, Centro Nacional de Analisis Genomico, CNAG-CRG, Center for Genomic Regulation. Barcelona, Spain. Sergi Beltran, Centro Nacional de Analisis Genomico, CNAG-CRG, Center for Genomic Regulation. Barcelona, Spain. Mads Emil Matthiesen, FindZebra APS, DK. Marion Poetz, Department of strategy and innovation, Copenhagen Business School, DK. Mats Hansson, Uppsala University, Sweden. Regina Trollmann, University of Erlangen, Germany. Emanuele Agolini, Ospedale Pediatrico Bambino Gesù, IRCCS, Rome, Italy. Silvia Ottobrino, Ospedale Pediatrico Bambino Gesù, IRCCS, Rome, Italy. Antonio Novelli, Ospedale Pediatrico Bambino Gesù, IRCCS, Rome, Italy. Enrico Bertini, Ospedale Pediatrico Bambino Gesù, IRCCS, Rome, Italy. Rita Selvatici, Unit of Medical Genetics, Department of Medical Sciences, University of Ferrara. Marianna Farnè, Unit of Medical Genetics, Department of Medical Sciences, University of Ferrara. Fernanda Fortunato, Unit of Medical Genetics, Department of Medical Sciences, University of Ferrara

#### Author contributions

AF, ESG and NG have elaborated the rationale and written the letter, all authors approved the final Manuscript.

#### Funding

S4C is a research project funded by EU-IMI under the grant agreement No 101034427.

#### Availability of data and materials

S4C website contains additional data and materials [www.screen4care.eu](http://www.screen4care.eu)

#### Declarations

#### Ethics approval and consent to participate

S4C (grant agreement No 101034427) has received full ethical approval by EU-IMI.

**Consent for publication**

All authors consented to publish this letter.

**Competing interests**

None.

Received: 3 January 2023 Accepted: 11 September 2023

Published online: 04 October 2023

**References**

- Green ED, Watson JD, Collins FS. Human genome project: twenty-five years of big biology. *Nature*. 2015;526(7571):29–31.
- Baynam G, Bowman F, Lister K, Walker CE, Pachter N, Goldblatt J, Boycott KM, Gahl WA, Kosaki K, Adachi T, Ishii K. Improved diagnosis and care for rare diseases through implementation of precision public health framework. *Rare Diseases Epidemiology: Update and Overview*; 2017. p. 55–94.
- Thompson R, Johnston L, Taruscio D, Monaco L, Bérout C, Gut IG, Hansson MG, 't Hoen PB, Patrinos GP, Dawkins H, Ensini M, Zatloukal K, Koubi D, Heslop E, Paschall JE, Posada M, Robinson PN, Bushby K, Lochmüller H. RD-Connect: an integrated platform connecting databases, registries, biobanks and clinical bioinformatics for rare disease research. *J Gen Intern Med*. 2014; 29 Suppl 3: S780–7.
- Zurek B, Ellwanger K, Vissers LELM, Schüle R, Synofzik M, Töpf A, de Voer RM, Laurie S, Matalonga L, Gilissen C, Ossowski S, Hoen PAC, Vitobello A, Schulze-Hentrich JM, Riess O, Brunner HG, Brookes AJ, Rath A, Bonne G, Gumus G, Verloes A, Hoogerbrugge N, Evangelista T, Harmuth T, Swertz M, Spalding D, Hoischen A, Beltran S, Graessner H; Solve-RD consortium. Solve-RD: systematic pan-European data sharing and collaborative analysis to solve rare diseases. *Eur J Hum Genet*. 2021 Sep; 29(9): 1325–1331.
- Therrell BL, Padilla CD, Loeber JG, Kneisser I, Saadallah A, Borrajo GJ, Adams J. Current status of newborn screening worldwide: 2015. *Semin Perinatol*. 2015;39(3):171–87.
- Wojcik MH, Zhang T, Ceyhan-Birsoy O, Genetti CA, Lebo MS, Yu TW, Parad RB, Holm IA, Rehm HL, Beggs AH, Green RC, Agrawal PB. BabySeq project team. Discordant results between conventional newborn screening and genomic sequencing in the BabySeq project. *Genet Med*. 2021;23(7):1372–5.
- Ceyhan-Birsoy O, Murry JB, Machini K, Lebo MS, Yu TW, Fayer S, Genetti CA, Schwartz TS, Agrawal PB, Parad RB, Holm IA, McGuire AL, Green RC, Rehm HL, Beggs AH. BabySeq project team. Interpretation of genomic sequencing results in healthy and ill newborns: results from the BabySeq project. *Am J Hum Genet*. 2019;104(1):76–93.
- Kingsmore SF, Smith LD, Kunard CM, Bainbridge M, Batalov S, Benson W, Blincow E, Caylor S, Chambers C, Del Angel G, Dimmock DP, Ding Y, Ellsworth K, Feigenbaum A, Frise E, Green RC, Guidugli L, Hall KP, Hansen C, Hobbs CA, Kahn SD, Kiel M, Van Der Kraan L, Krilow C, Kwon YH, Madhav Rao L, Le J, Lefebvre S, Mardach R, Mowrey WR, Oh D, Owen MJ, Powley G, Scharer G, Shelhutt S, Tokita M, Mehtalia SS, Oriol A, Papadopoulos S, Perry J, Rosales E, Sanford E, Schwartz S, Tran D, Reese MG, Wright M, Veeraraghavan N, Wigby K, Willis MJ, Wolen AR, Defay T. A genome sequencing system for universal newborn screening, diagnosis, and precision medicine for severe genetic diseases. *Am J Hum Genet*. 2022;109(9):1605–19.
- Pichini A, Ahmed A, Patch C, Bick D, Leblond M, Kasperaviciute D, Deen D, Wilde S, Garcia Noriega S, Matoko C, Tuff-Lacey A, Wigley C, Scott RH. Developing a national newborn genomes program: an approach driven by ethics, engagement and Co-design. *Front Genet*. 2022;30(13):866168.
- Veldman A, Kiewiet MBG, Heiner-Fokkema MR, Nelen MR, Sinke RJ, Sikkema-Raddatz B, Voorhoeve E, Westra D, Dollé MET, Schielen PCJ, van Spronsen FJ. Towards next-generation sequencing (NGS)-based newborn screening: a technical study to prepare for the challenges ahead. *Int J Neonatal Screen*. 2022;8(1):17.
- Downie L, Halliday J, Lewis S, Amor DJ. Principles of genomic newborn screening programs: a systematic review. *JAMA Netw Open*. 2021;4(7):e2114336. <https://doi.org/10.1001/jamanetworkopen>.
- Furnier SM, Durkin MS, Baker MW. Translating molecular technologies into routine newborn screening practice. *Int J Neonatal Screen*. 2020;6(4):80.
- Burke W. Genetic tests: clinical validity and clinical utility. *Curr Protoc Hum Genet*. 2014;24(81):915.
- Matthijs G, Souche E, Alders M, Corveleyn A, Eck S, Feenstra I, Race V, Sistermans E, Sturm M, Weiss M, Yntema H, Bakker E, Scheffer H, Bauer P. Guidelines for diagnostic next-generation sequencing. *Eur J Hum Genet*. 2016;24(10):1515.
- Angus J. Clarke, managing the ethical challenges of next-generation sequencing in genomic medicine. *Br Med Bull*. 2014;111(1):17–30.
- Souche E, Beltran S, Brosens E, Belmont JW, Fossum M, Riess O, Gilissen C, Ardesirdavani A, Houge G, van Gijn M, Clayton-Smith J, Synofzik M, de Leeuw N, Deans ZC, Dincer Y, Eck SH, van der Crabben S, Balasubramanian M, Graessner H, Sturm M, Firth H, Ferlini A, Nabbout R, De Baere E, Liehr T, Macek M, Matthijs G, Scheffer H, Bauer P, Yntema HG, Weiss MM. Recommendations for whole genome sequencing in diagnostics for rare diseases. *Eur J Hum Genet*. 2022;30(9):1017–21.
- Godard B, Schmidtke J, Cassiman JJ, Aymé S. Data storage and DNA banking for biomedical research: informed consent, confidentiality, quality issues, ownership, return of benefits. A professional perspective. *Eur J Hum Genet*. 2003;11(Suppl 2):S88–122.
- Bick D, Ahmed A, Deen D, Ferlini A, Garnier N, Kasperaviciute D, Leblond M, Pichini A, Rendon A, Satija A, Tuff-Lacey A, Scott RH. Newborn screening by genomic sequencing: opportunities and challenges. *Int J Neonatal Screen*. 2022;8(3):40. <https://doi.org/10.3390/ijns8030040>.
- Ulph F. What is health and what do we mean when we say an intervention improves health? *Eur J Hum Genet*. 2023. <https://doi.org/10.1038/s41431-023-01388-8>. (PMID: 37344573).

**Publisher's Note**

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

**Ready to submit your research? Choose BMC and benefit from:**

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more [biomedcentral.com/submissions](https://biomedcentral.com/submissions)

