Policy Insights Series

BIOMED21 COLLABORATION

Advancing Human-Centric Strategies for Rare Disease Therapeutics

The EU Perspective

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About the BioMed21 Collaboration

The Biomedical Research for the 21st Century (BioMed21) Collaboration is an international initiative dedicated to accelerating the transition toward human-relevant, predictive and ethical biomedical research. Its core mission is to advance scientific practices that better reflect human biology, improve translational success and reduce reliance on traditional animal-based models that often fail to capture the complexity of human disease. By promoting innovative tools such as organoids, microphysiological systems, computational modelling and other next-generation methodologies, BioMed21 aims to reshape the research and development ecosystem so that new therapies can reach patients more quickly, more safely and with greater precision.

As global health challenges grow more complex, from emerging infectious diseases to chronic and rare conditions, there is a pressing need for research strategies capable of generating insights that translate reliably into clinical benefit. Human-relevant technologies offer a path toward this goal, enabling richer mechanistic understanding, prevention research, more targeted therapeutic development and more efficient use of resources across the R&D pipeline. BioMed21 works with partners across regions and sectors to support the responsible integration of these approaches, combining scientific evidence, policy analysis and interest holder engagement to help modernize research frameworks in ways that are practical, equitable and future-oriented.

The policy papers in this series reflect this commitment. Each report examines how human-relevant technologies can be leveraged within specific regional and health contexts, identifying opportunities, gaps and policy pathways that can strengthen rare disease research and improve the development of innovative therapies. Together, they provide a shared foundation for governments, regulators, funders, researchers and patient communities seeking to improve research outcomes and translatability, advance public health and better address the diverse medical needs of populations worldwide.

This Policy Paper was developed in collaboration with Prof. Francesco Pappalardo (University of Catania; COMBINE Group)

Advancing Human-Centric Strategies for Rare Disease Therapeutics

The EU Perspective

Introduction

Rare diseases and their prevalence in the EU

Rare diseases are defined in the European Union as conditions affecting fewer than 5 individuals per 10,000. Ultra-rare diseases, often more complex and less researched, typically impact fewer than 1 in 50,000 people. While individually uncommon, these diseases collectively affect a substantial portion of the population. **In the EU, between 27 and 36 million people are living with one of over 6,000 to 8,000 known rare diseases**. A striking feature is their genetic basis, approximately 88% are linked to inherited or spontaneous genetic mutations. Moreover, the majority of these conditions – about 70% – manifest early in life, frequently during childhood[1].

Despite their societal impact, **most rare diseases remain without effective treatment**. For patients, this often means enduring long diagnostic journeys marked by misdiagnoses and fragmented care[2,3].

Rare diseases place a considerable burden not only on those affected and their families but also on healthcare systems. The EU has responded with initiatives such as the European Reference Networks (ERNs)[4], which support cross-border collaborations to improve diagnosis and care, and the EU Rare Disease (EU RD) Platform[5], which aims to strengthen disease registration and data sharing.

Rare disease classification

Rare diseases often present with multisystem involvement, variable severity, and complex genetic underpinnings, making conventional classification systems inadequate to fully capture their complexity.

To address this, Orphanet has developed a polyhierarchical structure that allows a single disease to appear in multiple categories simultaneously. This enables rare diseases to be visible in health records, registries, and research infrastructures. Orphanet's taxonomy also supports multiple axes of classification, including:

- Etiology (e.g., genetic, infectious)
- System involvement (e.g., neurological, dermatological)
- Inheritance pattern
- Mechanistic grouping (e.g., ciliopathies, lysosomal storage disorders)

1 https://www.europarl.europa.eu/RegData/etudes/STUD/2024/754210/IPOL_STU(2024)754210_EN.pdf
2 https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A52020SC0163
3 https://www.eurordis.org/information-support/what-is-a-rare-disease/
4 https://health.ec.europa.eu/rare-diseases-and-european-reference-networks/european-reference-networks_en
5 https://eu-rd-platform.jrc.ec.europa.eu/_en

This level of specificity is key for precision diagnostic, clinical trial design, and harmonised data reporting. As rare disease policy becomes increasingly data-driven, systems like Orphanet and their integration into regulatory frameworks and research funding programmes are central to delivering more coordinated and equitable care across the EU[1].

Notwithstanding significant investments, current research and development paradigms show limited translatability in rare diseases, largely due to their inability to capture human-specific mechanisms and inter-individual variability. This gap highlights the need for a systematic transition toward human-relevant approaches that can better support predictive and decision-oriented research.

Therapeutic Landscape for Rare Diseases in the EU

Despite two decades of dedicated policy and regulatory incentives, the number of approved therapies for rare diseases remains limited across the EU. As of early 2024, **less than 5% of all rare diseases** – roughly 307 out of 6,346 disorders – **benefit from at least one centrally authorised medicinal product with orphan designation**. In total, 184 medicinal products with orphan designation had received EU marketing authorisation by February 2023, and 410 additional medicines were authorised for rare indications without orphan designation by April 2024. While conditions like multiple myeloma benefit from multiple therapeutic options, with 12 authorised orphan products, the vast majority of rare diseases remain without any approved treatment.

The challenge is not only therapeutic scarcity but also **limited efficacy and large fragmentation**. Some drugs address only specific genotypes or narrowly defined clinical subgroups, leaving a significant portion of patients without effective treatment options. In addition, market authorisation at EU level does not guarantee availability across Member States as national reimbursement decisions and health system capacities vary.

Drug development for rare diseases faces numerous scientific and structural barriers. **For many conditions, no validated disease models exist**, particularly for ultra-rare or newly discovered syndromes.

Policy instruments such as the Orphan Medicinal Products Regulations (EC Regulation No. 141/2000), Horizon Europe, and the ERA4Health Partnership on Rare Diseases (ERDERA) (2024-2031) are designed to stimulate therapeutic innovation in this space. However, for meaningful progress, **funding programmes must actively prioritise the development, validation, and regulatory integration of innovative patient-relevant tools**.

Human-relevant approaches for rare diseases

Human-relevant models and tools in rare disease research

Traditional animal models are poorly suited to reproduce the genetic complexity, heterogeneity, and human-specific disease mechanisms that are common in rare diseases, especially in neurology, immunology, and developmental disorders[2].

These limitations underline the **need for alternative research and development strategies**, particularly those based on **human-relevant tools**. Complex in-vitro models (CIVMs), including organoids and organ-on-chip platforms, alongside *in silico* technologies, such as AI-based disease simulations or virtual patient models, and high-throughput screening approaches offer scalable and more predictive solutions to

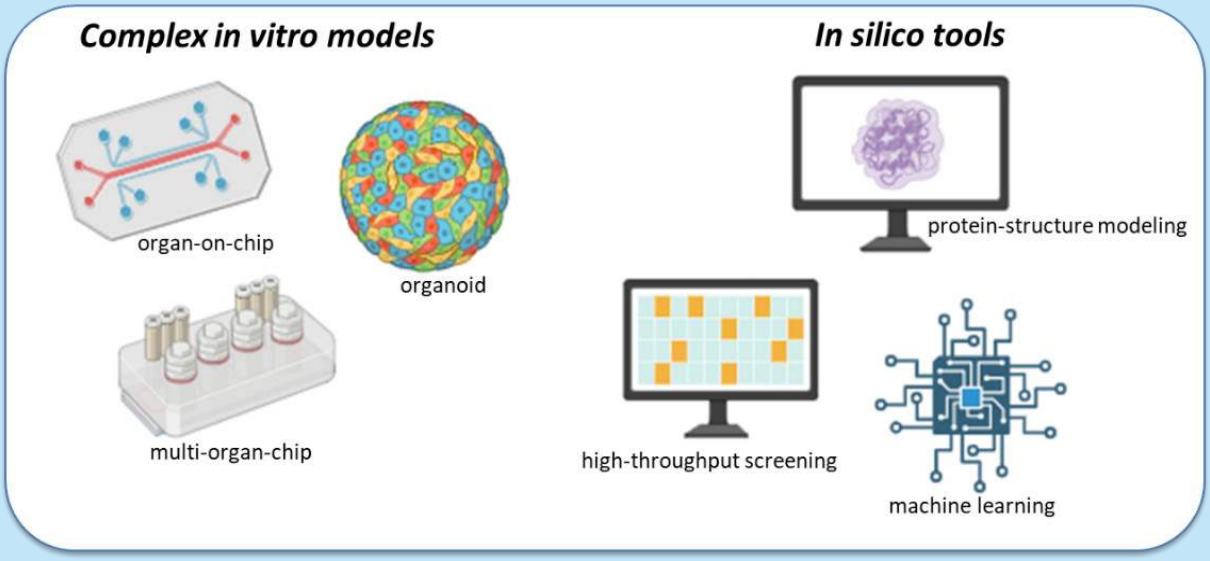
1 https://www.orpha.net/en/disease/classification/heads

2 https://www.cell.com/cell-stem-cell/fulltext/S1934-5909(21)00172-7 https://ojrd.biomedcentral.com/articles/10.1186/s13023-022-02557-6

PHOTO CREDIT: GUSTAVO FRING / PEXELS

Figure 1

Examples of complex in vitro models and in silico technologies available for rare disease research and drug discovery (created in https://BioRender.com)



these long-standing bottlenecks.

CIVMs are preclinical systems built from human-derived cells and tissues. These include patient-derived induced pluripotent stem cells (iPSCs), organoids, and organ-on-chip platforms that emulate the structure and function of human organs. **CIVMs offer an unprecedented capacity to model disease pathology in a way that reflects both genetic variability and tissue-specific context**[1]. They have already demonstrated their utility across a range of rare diseases, including spinal muscular atrophy, Gaucher disease, cystic fibrosis, and Duchenne muscular dystrophy, helping to uncover disease mechanisms, predict patient-specific responses, and evaluate potential therapeutic interventions[2,3,4,5].

These models can serve different roles across the research continuum, from hypothesis generation to predictive assessment and, increasingly, decision support. Clarifying their intended use is essential to ensure appropriate development, validation, and application.

In parallel, *in silico* tools are proving instrumental in complementing biological modeling with computational precision. These technologies span a wide range, from AI-driven literature mining and protein-structure modeling to virtual patient simulations and multiscale disease modeling[6].*In silico* methods have also been used to classify genetic variants, identify druggable targets, model disease progression, and support clinical trial design[7,8]. Computational pipelines have already been used to accelerate diagnosis, stratify patients, and inform the repurposing of existing compounds (e.g., PandaOmics[9,10]).

While these data-driven approaches have shown considerable promise, their applicability in rare diseases remains constrained by limited data availability and challenges related to interpretability and generalisability.

1 https://www.frontiersin.org/journals/cell-and-developmental-biology/articles/10.3389/fcell.2025.1526306/full
2 https://academic.oup.com/hmg/article-abstract/24/20/5775/557398?redirectedFrom=fulltext
3 https://www.nature.com/articles/nm.3201
4 https://www.frontiersin.org/journals/cell-and-developmental-biology/articles/10.3389/fcell.2022.878311/full
5 https://www.mdpi.com/2079-7737/12/6/867
6 https://www.nature.com/articles/s41746-025-01452-1
7 https://www.pnas.org/doi/10.1073/pnas.2418407122
8 https://www.sciencedirect.com/science/article/pii/S0141813024044684?via%3Dihub
9 https://pharma.ai/pandaomics
10 https://www.frontiersin.org/journals/aging-neuroscience/articles/10.3389/fnagi.2022.914017/full

In this context, mechanistic and multiscale computational models — including quantitative systems pharmacology, agent-based models, and emerging digital twin approaches — provide a complementary and often critical perspective[1]. By explicitly integrating biological knowledge and capturing disease mechanisms and inter-individual variability, these models can support the interpretation of sparse data and enable predictive simulations more directly aligned with decision-making needs.

From a regulatory standpoint, this distinction is particularly relevant. Approaches that combine data-driven insights with mechanistic understanding are increasingly seen as more robust and transparent, thereby better supporting regulatory evaluation and decision-making processes.

Especially when **combined together, CIVMs and *in silico* strategies represent a powerful shift toward predictive, personalised, and ethically responsible research tools**.

Human-relevant models and tools in rare disease drug discovery

CIVMs and *in silico* approaches are reshaping the way therapies for rare diseases are discovered and developed. These tools enable:

- early identification of therapeutic targets
- personalised compound screening
- prediction of clinical outcomes

In cystic fibrosis, patient-derived organoids have been used to stratify individuals for CFTR modulator therapy and to identify responders to existing drugs, leading to broader market approval[2,3].

In Fabry disease, kidney organoids enabled the testing of enzyme replacement strategies in a genetically defined context[4].

For Duchenne muscular dystrophy, 3D skeletal muscle models derived from iPSCs allowed testing of corticosteroids and gene therapies with patient-relevant endpoints[5].

Complementing biological systems, AI-driven drug repurposing platforms and molecular docking simulations have identified novel targets and compounds for lysosomal storage disorders, cystic fibrosis, and others[6,7].

Advanced modelling frameworks like Quantitative Systems Pharmacology (QSP) and Physiologically Based Pharmacokinetics (PBPK) are already informing dose selection and trial design[8,9,10].

These examples highlight how **CIVMs and *in silico* tools are not only generating knowledge but actively driving the development of rare disease therapeutics** tailored to individual biology. Beyond knowledge generation, these approaches are progressively contributing to decision-making processes in drug development, particularly where traditional evidence generation is constrained by small patient populations.

Programs and Initiatives supporting Human-Centred Rare Disease Research

European programs and initiatives

Across the European Union, several strategic initiatives and funding programs have been established to support the development and integration of human-relevant, non-animal technologies to address the unmet needs in rare diseases and therapy development. Together, these initiatives help strengthen scientific capacity, improve data integration and accelerate translational research across Member States.

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1 https://www.nature.com/articles/s41746-025-02068-1

2 https://www.nature.com/articles/nm.3201

3 https://www.cysticfibrosisjournal.com/article/S1569-1993(23)00067-X/fulltext

4 https://www.nature.com/articles/s12276-021-00683-y

5 https://www.pnas.org/doi/full/10.1073/pnas.2022960118

6 https://www.sciencedirect.com/science/article/pii/S2214426919300655?via%3Dihub

7 https://www.pnas.org/doi/10.1073/pnas.2418407122

8 https://jpharmsci.org/article/S0022-3549(23)00274-5/abstract

9 https://link.springer.com/article/10.1007/s10928-023-09874-8

10 https://link.springer.com/article/10.1007/s10928-024-09912-z

Table 1

Exemplary key EU-based Programs and Initiatives

Initiative/ Program	Description and Focus	Relevance to Rare Disease
Horizon Europe – ERDERA Partnership	A dedicated European partnership aimed at advancing research on rare diseases across EU Member States	Promotes patient-centric research including the use of CIVMs for modelling rare diseases and accelerating therapy development
Horizon Europe Call: "Development of New Effective Therapies for Rare Diseases"	Targeted funding opportunity under Horizon Europe	Explicitly supports research into human-relevant models for therapy development in rare diseases
HIT-CF Europe Project (Horizon 2020)	Human Individualised Therapy for Cystic Fibrosis	Uses patient-derived intestinal organoids from over 500 individuals with rare CFTR mutations to stratify patients and evaluate the efficacy of novel CFTR modulators (e.g., NCT06468527).
INVENTS	Horizon Europe project developing digital twins and virtual trial environments	Enables simulation of disease progression and treatment response in small patient populations
ERAMET	Horizon Europe initiative building a federated AI/ML pipeline for drug discovery	Uses *in silico* drug repurposing and multi-omics for rare disease drug target identification
RealiseD	Innovative Health Initiative project on digital evidence generation	Applies digital trial design to ultra-rare diseases where conventional trials are unfeasible
DREAMS	EU project using AI to identify repurposing candidates for neuromuscular diseases such as Duchenne and Pompe disease	Leverages *in silico* systems biology to map therapeutic targets and assess drug repositioning
Virtual Human Twins Initiative	Initiative to build supercomputing-based digital twins of human biology	Supports development of advanced virtual patient models and predictive *in silico* simulations

While these initiatives demonstrate strong momentum, challenges remain in terms of fragmentation, lack of standardisation, and limited interoperability across platforms and data sources. Addressing these gaps will be critical to fully realise the potential of human-relevant approaches at scale.

International Policy Pathways

Several countries have established dedicated regulatory pathways to accelerate the development of novel and innovative tools for developing drugs for rare diseases.

Table 2

Region/ Regulator	Key Mechanism Supporting Rare Disease & NAM research	Relevance for the EU
United States (FDA)	▪ START Pilot Program for high-touch advice for rare diseases ▪ RDEA for novel endpoint development ▪ ISTAND for qualifying innovative tools (e.g., liver-on-a-chip for DILI)	Provides models for structured early regulatory advice, co-development of endpoints and acceptance pathways for MPS/organoids.
European Union (EMA)	▪ Innovations Task Force & Scientific Advice ▪ Qualification of Novel Methodologies (QoNM) ▪ PRIME for high unmet need ▪ Conditional Marketing Authorisation	Highlights need for broader uptake of human-relevant evidence across Member States; provides foundation for expanding harmonized guidance, validation frameworks and cross-border evidence use within European Reference Networks.
United Kingdom (MHRA)	▪ Innovative Licensing and Access Pathways (ILAP) ▪ Innovation Passport + Target Development Profile ▪ Access Consortium work-sharing	Offers model for integrated regulatory-HTA[1] dialogue, which can inform EMA-HTA joint scientific consultations; relevant for improving coordinated assessment and uptake of therapies for very small patient groups.
Japan (PMDA/ MHLW)	▪ Orphan incentives (priority consultation, tax credits, grants) ▪ SAKIGAKE designation (expedited review) ▪ Conditional Early Approval	Illustrates regulatory flexibilities suited to ultra-rare conditions; highlights strategies the EU could mirror to accelerate access in areas of high unmet need, including adaptive approval mechanisms and targeted incentives.
China (NMPA/ CDE)	▪ Priority Review & Conditional Approval ▪ Hainan Lecheng RWE[2] pilot[3] for urgent needs ▪ Draft rare-disease guidance with risk-based CMC flexibilities	Demonstrates the use of real-world evidence pilots, pragmatic CMC[4] approaches and accelerated pathways; relevant for EU efforts to expand RWE integration and reduce approval timelines for rare diseases.

A key priority moving forward will be to align these regulatory pathways with emerging scientific approaches, ensuring that innovative models can be assessed in a transparent, fit-for-purpose manner and integrated into decision-making processes.

1 Health-Technology Assessment

2 Real-World Evidence

3 https://pubmed.ncbi.nlm.nih.gov/36653783/

4 Chemistry, Manufacturing and Controls

Key Policy Recommendations

Acceleration of rare disease therapeutics in the EU

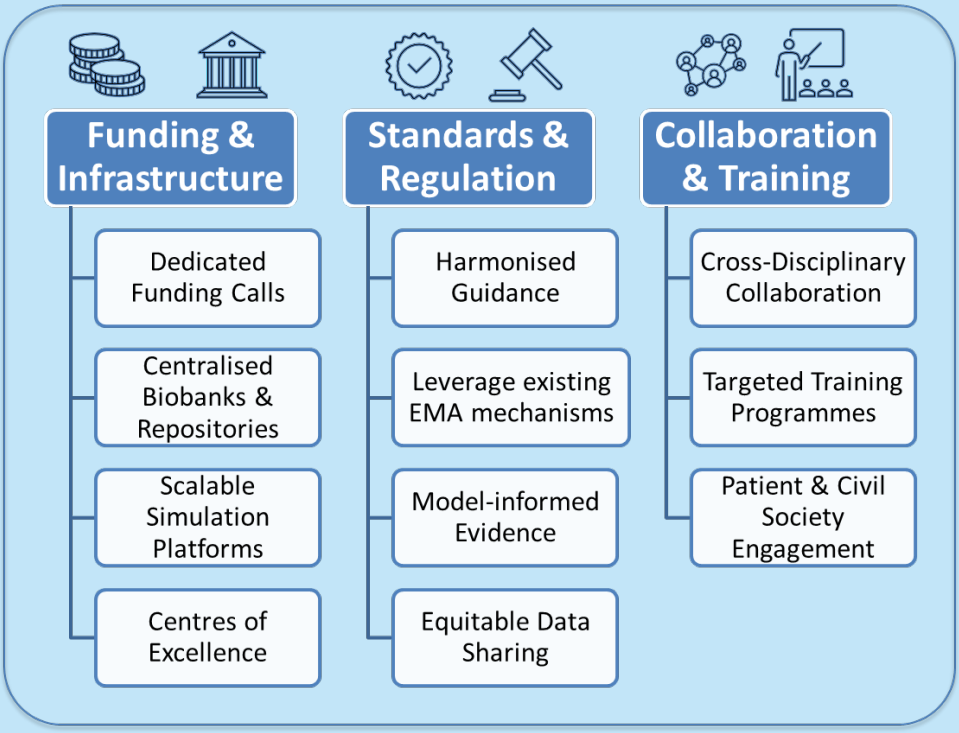
To unlock the full potential of complex in vitro and *in silico* models in rare disease research and drug development, the following priority areas should be addressed in the future EU funding programmes and policy strategies:

1. **Establish dedicated funding calls** for the development and integration of CIVMs and *in silico* tools specifically targeting rare diseases, under programmes like Horizon Europe, EU4Health, and the Innovative Health Initiative.
2. **Create centralised biobanks and high-quality data repositories** for patient-derived cells, organoids, and digital disease models to ensure accessibility, standardisation, and reuse across Member States.
3. **Develop and harmonise regulatory guidance and validation protocols** for CIVMs and *in silico* tools at the EU level to ensure their acceptance in drug development and authorisation processes.
4. **Build on existing EMA mechanisms** such as scientific advice and qualification pathways.
5. **Promote cross-disciplinary collaboration** between developers of CIVMs, AI and modeling experts, clinicians, and regulators to co-design human-relevant disease models and translation platforms.
6. **Invest in scalable infrastructures and simulation platforms**, such as virtual patient cohorts and digital twins, to support personalised drug development, and include its structured use in regulatory interactions and evidence generation strategies.
7. **Incentivise the use of model-informed evidence** in regulatory decision-making and promote its inclusion in EMA scientific advice and qualification pathways.
8. **Support the creation of Centres of Excellence** for CIVMs and *in silico* development to pool expertise, offer training, and foster uptake across academia and SMEs.
9. **Ensure equitable and inclusive data sharing**, including geographical, ethnic, and socioeconomic representation, using ethical frameworks and secure platforms (e.g. secure distributed data systems).
10. **Develop targeted training programmes** for researchers, regulators, and clinicians in the use, interpretation, and co-development of advanced human-centric tools.
11. **Engage patients and civil society** in the design, evaluation, and governance of CIVM and *in silico* initiatives to ensure alignment with real-world needs and foster trust in innovation.

PHOTO CREDIT: ADITYA ROMANSA / UNSPLASH

Figure 2

Key recommendations to speed rare disease therapeutics in the EU



Conclusions

Europe stands at a pivotal moment in the advancement of rare diseases therapeutics. While decades of policy action and research funding have improved awareness, coordination and infrastructure, the vast majority of rare diseases remain without effective treatment. Traditional R&D approaches, heavily reliant on animal models and limited by population size and disease heterogeneity, have proven insufficient to meet the growing and urgent needs of rare disease patients.

Human-centric technologies, particularly CIVMs and *in silico* approaches, are increasingly reshaping the landscape of rare disease research. These tools enable mechanistic insights, patient-specific modeling and predictive data integration, even in the absence of large clinical cohorts. Their integration into EU-funded projects and clinical pipelines has already begun, with strong early signals of feasibility and impact.

To build on this momentum, future EU research and innovation strategies must prioritise the development, validation, and regulatory integration of these state-of-the-art methodologies. Dedicated funding, regulatory support, cross-border collaboration, and meaningful patient engagement are essential to scale their use. Moreover, policy instruments must ensure that the outputs of these tools are interoperable, ethically governed, and accessible across Member States.

Europe has the scientific capacity, technological foundation, and regulatory openness to lead globally in the development of more efficient and personalised therapies for rare diseases. By investing in human-relevant models and embracing innovation, the EU can dramatically accelerate progress for millions of underserved patients, while setting a global benchmark for responsible, forward-looking biomedical research. Without a structured integration of these approaches into research and regulatory frameworks, the current gap in rare disease therapeutics is unlikely to close.

Our mission

The Biomedical Research for the 21st Century (BioMed21) Collaboration—comprised of an international team of scientists, policy specialists, and communications experts—works in partnership with academic institutions, governments, charities, agencies, and the corporate sector to advance and promote human-centric nonanimal science research.

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