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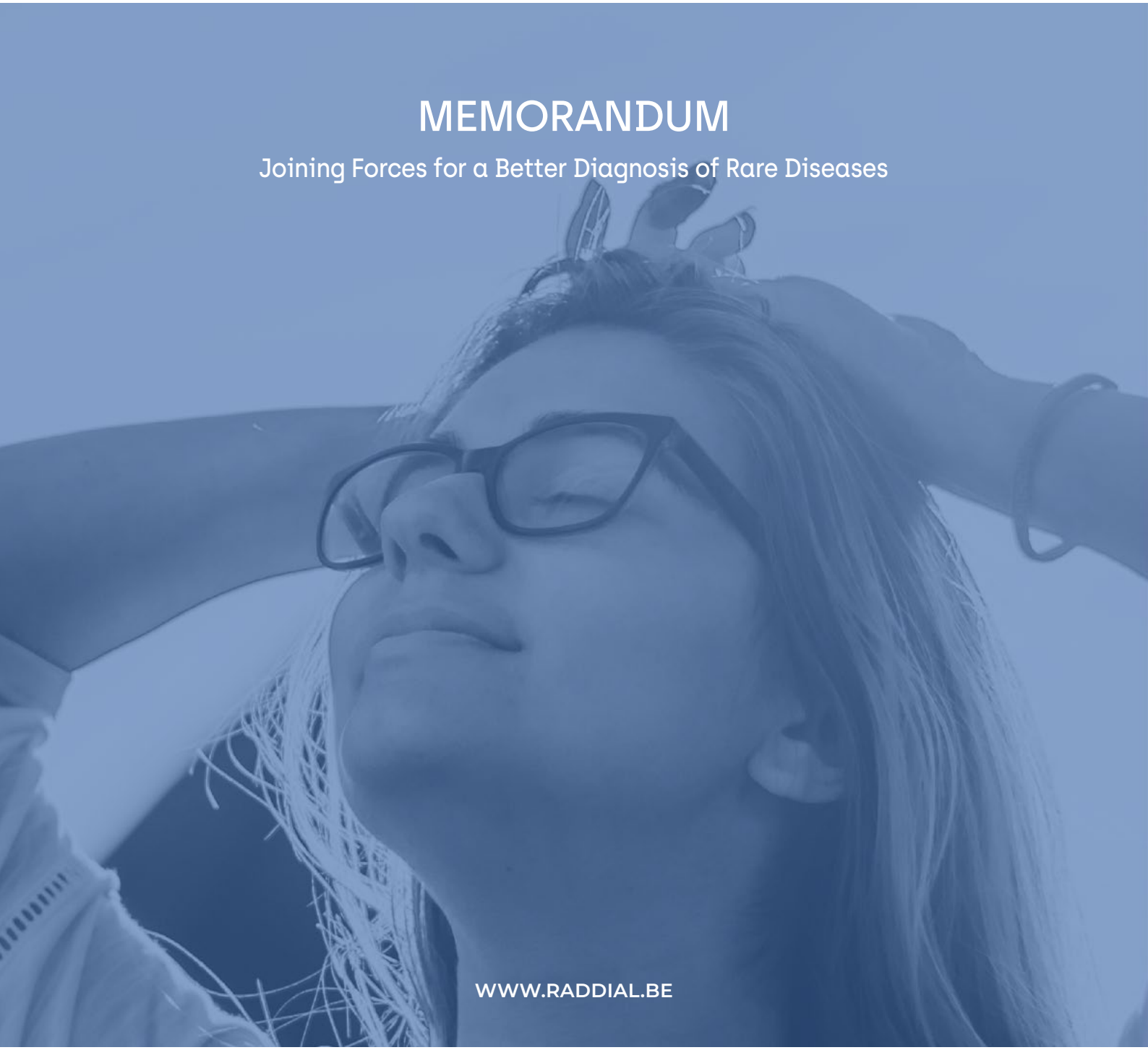
RARE DISEASE DIAGNOSIS ALLIANCE

MEMORANDUM

Joining Forces for a Better Diagnosis of Rare Diseases



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How to optimize and shorten the diagnosis pathway for rare disease patients?

12 policy recommendations

In recent years, public awareness on rare diseases has undeniably increased. The National Plan for Rare Diseases, launched in 2013, has led to advancements in several key areas, but some important actions in the 4 defined domains have not or not completely been implemented. Thanks to the continued efforts of the Koning Boudewijnstichting, Rare Diseases Belgium (RaDiOrg), the health committee of the federal parliament and various other stakeholders, rare diseases have nevertheless remained on the policy agenda.

Despite the progress made, major challenges remain in the realm of rare diseases, particularly with regard to obtaining a timely and accurate diagnosis of a rare disease. The current average timeframe between the first sensation of symptoms and the final diagnosis of a rare disease is 4,9 years[1]. This long and arduous diagnosis process is rightfully a source of frustration – not only for the patient who is deprived of appropriate treatment (if it exists) for too long, but also for physicians who want the best for their patient. From the government's point of view, the long search for a correct diagnosis is also problematic, because a late diagnosis often also implies a treatment that is suboptimal.

In order to address this challenge, the Rare Disease Diagnosis Alliance (RADDIAL), was founded in the course of 2022. The alliance consists of Sanofi, Takeda, Janssen, Alnylam Pharmaceuticals and Chiesi. By means of a series of roundtable conferences, RADDIAL brought together patient representatives, academic experts, physicians and health insurance providers for a collaborative dialogue, resulting in the development of concrete policy recommendations for a faster diagnosis of rare diseases in Belgium.
These 12 recommendations, clustered in four thematic areas, are listed in this memorandum..

1. IMPROVING AWARENESS AND KNOWLEDGE

Considering that. . .

- There is a continuously growing set of data, models and tools that can support the diagnosis of rare diseases, but which remains highly fragmented and therefore insufficiently known or accessible.

- Rare diseases are not systematically integrated into the medical and pharmaceutical curriculum at universities, missing the opportunity to raise awareness among future clinicians in an early stage.

- The time-to-diagnosis can be significantly shortened if clinicians adopt a 'think rare' approach when faced with symptoms that are vague, unclear and challenging to interpret.

- It is unrealistic to expect all clinical practitioners to be familiar with all of the more than 7.000 known rare diseases, which are often multi-systemic conditions, so that patients often have to go to different practitioners and thus do not benefit from centralized care.

- The federal government acknowledges the significant unmet needs in the field of rare diseases and stresses the importance of developing an action plan as part of its integrated care approach. This plan should focus on identifying expertise, improving care coordination, increasing accessibility, fostering the development and sharing of knowledge in the field of rare diseases[2].

We ask policymakers to. . .

1 **Establish a working group for the development of a digital 'Rare Disease Diagnosis Toolbox' intended for general practitioners, pharmacists, and other clinical practitioners who might encounter patients with symptoms that may be indicative of a rare disease.**

This (online) toolbox should essentially be interoperable and designed as a resource library with accessible information and easy-to-implement instruments that facilitate diagnosis of rare diseases (e.g. decision tree templates, red flags, etc.). The development of such a toolbox should be done in close collaboration with first-line healthcare professionals' associations, physicians' associations, pharmacists' associations, and patients' associations.

Other features to be integrated in the toolbox include:
- Artificial Intelligence-powered diagnosis tools.
- Links to platforms for collaborative diagnosis among clinical practitioners (e.g. within the networks of the Lokale Kwaliteitsgroepen/ Groupes locaux d'évaluation médicale (LOK/GLEM) networks)[3].
- Links to Rare Disease Functions in hospitals across Belgium.

2 **Support professional associations in the development of targeted training modules** for general practitioners and other first-line healthcare actors, aimed at increasing their knowledge of rare diseases, red flags, diagnosis procedures for rare diseases and access to care. Next to that, emphasize the clinical importance of an early diagnosis and its positive impact on the overall healthcare system. These training modules should also instruct healthcare professionals on the existence and application of data driven artificial intelligence models. General practitioners and other first-line healthcare actors - including pharmacists - should be incentivized to participate in these training modules by means of an appropriate accreditation program. This initiative should complement the current initiative[4] by the Foundation Roi Baudouin to raise awareness about rare diseases among first- and second-line healthcare professionals.

3 **Include education on rare diseases as an ideally mandatory or otherwise elective course in medical and pharmaceutical curricula at Belgian universities** and offer courses on rare diseases in continued medical and pharmaceutical education programs. While this is at the full discretion of the universities, the competent authorities at the level of the regions and communities could create the right environment for this, e.g. by making it a mandatory requirement for the evaluation of university curricula in the near future.

2. NEWBORN SCREENING AND GENETIC TESTING

Considering that. . .

- Newborn screening is a powerful and reliable tool for detecting rare diseases in an earlystage.

- The current newborn screening programs do not include a full range of diseases that potentially could be detected.

- The federal government explicitly acknowledges the importance of a timely inclusion of rare diseases for which a treatment is available in regional screening programs[5]. To this end the regions will be systematically informed on treatments for rare diseases that are in the process of being approved.

- From a social justice and equity perspective, access to newborn screening programs in Belgium should not depend on the region where a child lives.

- Continuous advanced research can offer a lot of opportunities for newborn screening by the inclusion of genetic testing. For example: the recently launched pilot project 'Baby Detect' at CHU Liège, which screens for 120 diseases[6], and the implementation of Whole Exome Sequencing[7] or Whole Genome Sequencing[8] in Neonatal Intensive Care Units.

- The existence of the BeGECS test (the Belgian Genetic Expanded Carrier Screening) which can detect over 1,200 hereditary diseases, for individuals who would like to know if they carry a genetic mutation that could be passed on to their offspring.

- The advice of the Belgian Superior Health Council (2017)[9] regarding the Reproductive Genetic Carrier Screening (RGCS), outlining specific recommendations to ensure a responsible implementation of RGCS in Belgium.

- Genetic screening is not part of any generalised screening program for the general population.

We ask policy makers to. . .

4 **Expand newborn screening programs to all traceable and treatable diseases, based on the advice of a to-be-created inter-federal multidisciplinary team.** The scope of the newborn screening program should be determined upon recommendation of a multidisciplinary team consisting of genetic experts, screening experts and patients, with priority given to treatable diseases and openness to other cases where symptoms can be mitigated to improve the patient's quality of life. A decision to approve such a program could be taken quite quickly.

5 **Harmonize the decision-making processes across regions and at the federal level** for newborn screening, to achieve equal opportunities, equal outcomes, and equal quality of care across all regions. Further (mandatory) collaboration between regions and the federal level on newborn screening is necessary.

6 **Enhance the potential of genetic testing by:**

a. **Facilitating genetic testing for the validation of rare disease diagnoses with patients suspected of having a rare genetic disease** by identifying the specific genetic mutation causing the disease if no biomarkers are available. This approach can enhance the accuracy of diagnosis, particularly in cases with atypical symptoms or late onset.

b. **Pursuing and supporting the continuous research and development of genetic testing**, and consider the implementation of new promising methodologies.

c. **Studying the expansion of reimbursement of genetic testing, for example for the Belgian Genetic Expanded Carrier Screening (BeGECS) test for at-risk couples.**

d. **Conducting international and regional benchmarks to determine best practices with regards to genetic screening**, to help determine which healthcare professionals should recommend patients for genetic screening.

e. **Increasing broad societal support for genetic testing and its benefits through education**.

3. THE ROLE OF RARE DISEASE FUNCTIONS

Considering that. . .

- The tremendous potential of Rare Disease Functions can probably not be fully developed in the absence of a specific identification as centers with required expertise.

- The federal government recognizes the need for patients to have access to qualitative care provided by centers with required expertise[10].

- The federal government recognizes the importance of the central data register for rare diseases and considers an increased participation in data registration as a policy priority[11].

- The King Baudouin Foundation recommends the development of a state-of-the art rare disease registry allowing, within the limits of existing data regulation, a swift information exchange, stimulating scientific research, facilitating the development of an evidence-based rare disease policy and increasing the quality of care[12].

- The federal government intends (as part of the hospital landscape reform) to concentrate care for complex conditions (including rare diseases) that require the pooling of expertise in a limited number of reference points at supra-regional level[13].

- The federal government is pooling efforts on the creation of a new Belgian Health Data Authority[14], with the aim to facilitate access to available health data and health-related data in a reliable and simplified manner.

- Currently, Sciensano has registered ca. 1% of rare diseases after seven years of managing this registry, despite their dedicated efforts and strong expertise.

We ask policy makers to. . .

7 **Encourage (financially) the existing Rare Disease Functions[15] in accelerating and expanding the sharing of knowledge and expertise with peripheral centres and first-line healthcare professionals.**

8 **Stimulate the coverage and systematic update of the Central Rare Disease Registry at the national level**, building on expertise from and in line with European initiatives (e.g., The ERN's Rare Disease Registries), and further expanding the data collection from the genetic centers to the Rare Disease Functions and ERNs. The recently created Belgian Health Data Agency offers the momentum to do so, in partnership with the soon to be created European Health Data Space and the ERNs. Further increasing coverage by means of privacy enhanced technology like Federated Learning could be worthwhile to investigate as well.

9 **Make all available data of existing Rare Disease Registries accessible to the broader research community of academics, health care providers and researchers in the industry**, in accordance with the FAIR-principle (Findable, Accessible, Interoperable, Reusable) to support A.I.-based diagnoses and stimulate clinical research. On the Belgian level, the new Health Data Agency should be an important enabler in this process.

4. AN INTEGRATED CARE TRAJECTORY

Considering that. . .

Diagnosis of a rare disease often requires interdisciplinary collaboration between General Practitioners (GPs) and other clinicians. However, this is currently not incentivized. There is no financial compensation foreseen to cover the coordination time invested by multiple clinicians.

The federal government recently launched a new Patient-centered Integrated Care Inter-federal Plan[16], in which consultation, dialogue and collaboration between all the care providers is key. This includes among other things a 'New Deal' with GPs in which financial incentives are foreseen for, among other things, multidisciplinary collaboration[17].

The King Baudouin Foundation recommends the development and implementation of an integrated care model with, among other things, the possibility of interdisciplinary consultation[18].

Tools and models exist to facilitate and optimize information exchange between healthcare professionals, but their existence is insufficiently known.

We ask policy makers to. . .

10 **Stimulate and facilitate interdisciplinary consultations** between all involved healthcare providers for patients suspected of having a rare disease. This incentive should cover in-person and remote consultations.

11 **Promote the adoption and the use of digital tools that facilitate communication, cooperation, and referrals for genetic testing between healthcare professionals in the different lines.** The adoption of Prisma in the Netherlands serves as an illustration of this proposal. This promotion should ideally be done by the medical associations.

12 **Support the setup of a pilot project related to the designation of a group of GPs who can serve as 'reference persons'** for their peers regarding rare disease-related questions. These reference doctors would serve as the liaison between, on the one hand, healthcare professionals, and on the other hand, relevant experts and the Rare Disease Functions. They would report on a yearly basis on trends and issues to the Federal Public Service Public Health and receive an additional honorarium for their role.

The policy recommendations presented in this Memorandum were identified and developed during two Roundtable Sessions in September and October 2022, with the active involvement of a wide range of experts in rare diseases, including patient representatives, academic experts, physicians and health insurance companies. The Roundtable sessions were organized at the initiative of the Rare Disease Diagnosis Alliance (RADDIAL) composed of five pharmaceutical companies: Takeda, Sanofi, Janssen, Chiesi and Alnylam. Through this initiative, the involved companies wish to take their responsibility and contribute to an improvement of the predicament of patients with a rare disease in Belgium.

This policy recommendations contained in this Memorandum are validated and endorsed by the individuals listed below:

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References

[1] Source: Eurordis, "Rare Barometer Survey", 2022

[2] "Mijn beleidsplan inzake zeldzame ziekten focust op identificatie en concentratie van expertise, zorgcoördi-natie, toegankelijkheid en kennisontwikkeling en -deling", Beleidsnota Volksgezondheid, 28/10/2022, pag. 49

[3] Cf. the 'Medics for Rare Disease' project in the UK www.m4rd.org

[4] Koning Boudewijnstichting, Project call: Raising awareness about rare diseases for primary and secondary care providers, Sensibilisering over zeldzame ziekten voor zorgverleners in de eerste en tweede lijn | Koning Boudewijnstichting (kbs-frb.be)

[5] "To ensure that rare diseases for which a drug is available can be included in the screening programs of the regions in a timely manner, we will optimize the exchange of information between the federal government and the regions", Policy Note Public Health, 28/10/2022, p. 51

[6] www.babydetect.com

[7] Medical costs of children admitted to the neonatal intensive care unit: The role and possible economic impact of WES in early diagnosis. European Journal of Medical Genetics, Volume 65, Issue 6, May 2022. https://www.sciencedirect.com/science/article/pii/S1769721222000489

[8] https://www.mdpi.com/2141718

[9]https://www.hgr-css.be/en/report/9240/carrier-screening

[10] "In order for every person in Belgium suffering from a rare disease to be entitled to quality care in the centre or centres with the necessary expertise, RIZIV agreements for rare diseases will be concluded, based on a generic framework". Policy Note Public Health, 28/10/2022, p. 50

[11] "The follow-up of rare diseases is done by the Central Register of Rare Diseases (CRRD). The first priority there is to increase participation in the registry, by expanding data collection and by increasing registration from the genetic centres". Policy Note Public Health, 28/10/2022, p. 51

[12] KBS, Care for people with rare conditions. State of affairs and recommendations, recommendation 3, p.31

[13] "My policy plan on rare diseases focuses on identification and concentration of expertise, care coordination, accessibility and knowledge development and sharing", Policy Note Public Health, 28/10/2022, p. 34

[14] Moniteur belge, 14/03/2023: Law establishing and organising the Health Data Agency?

[15] i.e., the seven university hospitals and the Institut de Pathologie et de Génétique at the Grand Hôpital de Charleroi

[16]https://www.riziv.fgov.be/nl/professionals/info-voor-allen/het-interfederaal-plan-voor-geintegreerde-zorg

[17] "This model should … (4) correctly reimburse GPs for tasks during and outside consultations, (5) allow task delegation, (6) set the right incentives, including on prevention, population management, multidisciplinary cooperation, quality, availability, etc.", Policy Note, 28/10/2022, p. 51

[18] KBS, Care for people with rare conditions. State of affairs and recommendations, recommendation 2, p. 30

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