



SEP Research Evaluation 2016-2020
Princess Máxima Center for Pediatric Oncology

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1. Foreword by the committee chair

It is with great pleasure that I present this evaluation report of the Princess Máxima Center for Pediatric Oncology that was composed on basis of the site visit the committee conducted on November 3 and 4, 2021.

On behalf of all of the committee members I can say that it was a great pleasure to encounter such a positive and collaborative spirit in the Center. We were offered a chance to meet with employees from many different divisions, including clinicians, researchers and supporting staff. All of those meetings had one thing in common, a very strong sense of a common goal. The leadership of the Center can be proud of the mission-oriented culture it has managed to establish in the relatively brief period since the inception of the Center.

We were also impressed with the quality of the overall research program and the level of quality of young talents that the Center has managed to attract. This is an exceptional achievement if one considers that this Center had to be established from scratch, and has been operational for only a few years. The committee was pleased to witness a high level of interaction between basic research and clinical practice, and would like to encourage leadership of the Center to continue to develop its M4C concept. The M4C model can help to bring together sufficient critical mass that will be essential to address the clinical needs that are presented by the rare pediatric cancers. Also, it is a great model to further enforce the mission-oriented culture of the Center.

The Princess Máxima Center for Pediatric Oncology has a unique position in the world, and this comes with an important responsibility to children with cancer. The committee encourages the Center to seek crossborder collaborations on all fronts, since this will be crucial to develop better treatments in pediatric oncology. Sometimes the Center could lead, while in other cases the Center could be a great facilitator of international consortia in pediatric oncology. It would be great if the Center could extrapolate the strong collaborative spirit that we sensed internally to the international consortia it engages in.

Much work still lies ahead of the Center, but we were pleased to hear that attention is being paid to attract expertise that is still lacking or underrepresented at the Center. Also, being a relatively new Center, some of the procedures were still under construction. Nonetheless, the Center is on a great trajectory, and has the growth potential to be able to solve these issues rather quickly.

In closing, I would like to express our deep respect for the parents whose efforts have resulted in the creation of the Princess Maxima Center for Pediatric Oncology. Your efforts have resulted in the creation of a Center that has the potential to lead the way towards effective treatments for all children with cancer.

On behalf of the entire evaluation committee,

René Medema

2. Procedure

2.1 Scope of the review

The Princess Máxima Center for Pediatric Oncology asked a review committee of external peers to perform a review of the research conducted over the period 2016-2020 in accordance with the Strategy Evaluation Protocol 2021-2027 (SEP) for research evaluations in the Netherlands. Due to Covid-19, this evaluation was postponed to 2021 and expanded to encompass 2016-2021. In line with the SEP, the evaluation was to include a backward-looking and a forward-looking component. The committee was asked to judge the performance of the research unit on the main assessment criteria specified in the SEP and to offer its written conclusions as well as recommendations based on considerations and arguments. The main assessment criteria are:

- Research Quality;
- Societal Relevance;
- Viability of the unit.

During the evaluation of these criteria, the committee was asked to incorporate four specific aspects relating to how the unit organizes and performs its research, to its composition in terms of leadership and personnel, and to how the unit is run on a daily basis. These aspects are:

- Open Science;
- PhD Policy and Training;
- Academic Culture;
- Human Resources Policy.

For more information on the criteria and categories of the Strategy Evaluation Protocol 2021-2027, see appendix 1.

Furthermore, the Princess Máxima Center specifically asked the committee to consider three terms of reference:

- Collaboration & integration;
- Talent and excellence programs;
- Spotless reputation.

2.2 Composition of the committee

The composition of the committee was as follows:

- Prof. dr. René Medema (chair), Director of Research, Chairman Board of Directors, Netherlands Cancer Institute;
- Prof. dr. med. Angelika Eggert, Director, Department of Paediatric Oncology and Hematology, Charité Universitätsmedizin Berlin;
- Prof. dr. med dr. rer nat Sabine Mueller, Professor of Neurology, Neurosurgery and Pediatrics, University of California San Francisco;

- Prof. Andrea Biondi, Professor of Pediatrics and Director, Department of Pediatrics, University of Milano-Bicocca;
- Prof. dr. Anne May, Professor of Clinical Epidemiology of Cancer Survivorship, University Medical Centre Utrecht;
- Prof. dr. Madelon Maurice, Professor of Molecular Cell Biology, UMC Utrecht;
- Dr. Puck Knipscheer, Principal Investigator, Hubrecht Institute;
- Marlies Ludikhuizen MSc, PhD student, UMC Utrecht.

The committee was supported by dr. Fiona Schouten, who acted as project coordinator and secretary on behalf of quality assurance agency Academion.

2.3 Independence

Personal or professional relationships between committee members and the research unit under review were reported and discussed at the start of the site visit amongst the committee members. The committee concluded that no specific risk in terms of bias or undue influence existed and that all members were sufficiently independent.

2.4 Data provided to the committee

The committee received the self-evaluation report from the unit under review, including all the information required by the SEP. It received both the original Research Self Evaluation Report 2019 and the Addendum SEP 2021, providing an update of the self-evaluation report to include 2019-2021.

The committee also received the following documents:

- The Terms of Reference;
- The SEP 2021-2027;
- Annual Research Reports 2017-2020;
- Focused and promising. The strategy of the Princess Máxima Center for pediatric oncology for 2020-2024.

2.5 Procedures followed by the committee

Prior to the first meeting, which was held online, all committee members independently formulated a preliminary evaluation of the units under review based on the written information that was provided before the site visit. In its first meeting, on 27 October 2021, the committee was briefed by the Academion secretary about research reviews according to the SEP 2021-2027. It discussed the preliminary evaluations and identified questions to be raised during the site visit. It agreed upon procedural matters and aspects of the evaluation.

The site visit took place on 2-4 November 2021 (see the schedule in appendix 2). The committee conducted interviews with representatives of the Princess Máxima Center. At the end of the visit, the committee discussed its findings and comments in order to allow the chair to present the preliminary findings and to provide the secretary with argumentation to draft a first version of the review report. The final evaluation was based on both the documentation provided by the Princess Máxima Center and the information gathered during the interviews with management and representatives of the research unit during the site visit.

The draft report by the committee and secretary was presented to the Princess Maxima Center for factual corrections and comments. In close consultation with the chair, the comments received were reviewed to draft the final report. The final report was presented to the Princess Maxima Center.

3. Executive summary

In this evaluation process, and during the site visit to the Princess Máxima Center, the review committee encountered an open and vibrant research community, including support staff and research facilities, which is entirely aligned with the Máxima's mission of curing every child with cancer while maintaining optimal quality of life. The committee agrees with this mission and considers the Princess Máxima Center a unique national care and research facility answering to an urgently felt need.

The committee highly appreciates the Máxima Comprehensive Childhood Cancer Center (M4C) structure, through which integration of care and research are targeted and achieved. However, the committee finds that Quality of Life could be better integrated in this M4C concept. It also points out that constructive criticism is necessary in the organization for optimal quality of care and research.

The recent adaptation of the HR and leadership structures in line with M4C is a good development, which needs some finetuning when it comes to providing talented junior and mid-career staff as well as postdocs with a stimulating and comfortable environment to develop and grow. Diversity and inclusivity have the attention of the Princess Máxima Center but could be made more effective by involving the entire organization, following the example of the internationalization initiative MIC. Patient and parent representation need to be compensated and supported for their crucial contribution to research at the Princess Máxima Center.

The committee concludes that in its brief period of existence, the Princess Máxima Center has performed exceedingly well, achieving excellent research output, excellent societal relevance, and outstanding viability once the financial situation improves and stabilizes as anticipated. The committee invites the Princess Máxima Center to consider focusing its growth and making conscious strategic choices that impact recruitment, HR, research, and (national and international) networking opportunities. It applauds the Center for everything that it has achieved so far.

4. Recommendations

Based on the evaluation summarised in chapter 3 and further motivated in chapter 5, the committee formulates the following recommendations for future development.

- *Ideal size and focused growth:* Growth of the institute will not continue on the exponential curve it was on since its inception, so now is the time for strategic decisions which areas of research will be prioritized. These decisions will have to be taken based on what areas the Princess Máxima Center thinks it can contribute most in the years to come. Make sure that all future room to grow is utilized to address “need-to-haves” rather than “nice-to-haves”.
- *Quality of Life:* The Princess Máxima Center is in a unique position to ensure that QoL is an integral aspect of all of the efforts to improve treatment of pediatric cancer. The Center needs to better incorporate QoL research in the M4C concept in the coming years, and make sure that the QoL data are integrated in the big data infrastructure.
- *Parent and patient representation:* Research at the Princess Máxima Center has been, and continues to be, indebted to the parent and patient representatives. It should cherish their ongoing dedication and involvement by creating a stronger support system for the parent/patient representatives involved with research, and organizing compensation for the considerable time and effort they put into the Máxima and its research.
- *HR and career support:* Finding and holding on to research talent is a top priority for the Princess Máxima Center, and it should continue developing a transparent and clear assessment and support system for postdocs, junior and mid-career scientists. Expand postdoc and early career positions and/or provide transparent links to further tenure track positions and offer them better career development opportunities by creating transparent policies for contract extensions, tenure track positions, and guidance towards alternative career tracks, in order to be able to also attract international research talent.
- *Sensitivity trainings:* Efforts to improve diversity and inclusion have limited reach in the organization in their current form. The Princess Máxima Center should invest in sensitivity trainings for all employees to raise awareness of underlying mechanisms and unconscious biases that form barriers to female researchers and/or other groups.
- *Community:* Encourage constructive criticism; the community spirit is fantastic, but make sure this doesn't stand in the way of expressing criticism towards each other's plans and research.

5. Research review of the Princess Máxima Center

5.1 Introduction

In 2018, the Princess Máxima Center for pediatric oncology opened at Utrecht Science Park. This marked the end of a ten-year trajectory where a group of parents (VKN; Vereniging Kinderkanker Nederland) worked with healthcare professionals (united in SKION) to create a national children's cancer center with the financial support of KiKa for the research. This was deemed necessary to make more and better progress in the field. Previously, the field of pediatric oncology was spread over various hospitals and research facilities, and the high variety of tumor types and relatively small number of patients (600 a year) made it challenging to study each form of cancer and develop improved care. Uniting care and research in one center could accelerate advances in treatment.

The actual start of the Princess Máxima Center was in 2014, with the treatment of the first patients (solid tumors) in a dedicated hired wing of the Wilhelmina Children's Hospital (WKZ) in Utrecht. The research department of 'the Máxima' started in 2016, on a rented floor of the Hubrecht Institute in the Utrecht Science Park. At the end of 2016, 14 research groups had started in the Princess Máxima Center. A major step forward was taken in June 2018, when 'the Máxima' officially opened its new building, integrating research and clinical care. The building is connected to the WKZ and the University Medical Center Utrecht (UMCU) by a bridge representing the interconnectedness of the Princess Máxima Center with these and other external partners.

At the time of the site visit, the number of individual research groups had grown to 36. In total, 450 employees are currently working in the research unit of the Princess Máxima Center. The Máxima is currently the only childhood cancer center in Europe of this size, and it occupies a unique position due to its nationwide, collaborative profile.

5.2 Profile, Strategy and Management

Profile and strategy

The mission of the Princess Máxima Center is to cure every child with cancer while maintaining optimal quality of life. This is an ambitious mission, as 25% of children diagnosed with cancer do not survive. To achieve its goals and mission, the Princess Máxima Center has translated its vision into six key strategic objectives for the entire organization, both the clinic and research branches, over the 2020-2024 period. These objectives are (1) The Máxima Comprehensive Childhood Cancer Center (M4C); (2) Innovative diagnostics and treatment (specifically in immune-oncology & neuro-oncology); (3) Quality of life; (4) State-of-the-art data provision; (5) Recruit, train and retain top experts; and (6) Internationalization. Besides these defined targets, which will be touched upon throughout this report, the Princess Máxima Center has identified three major areas that are of importance in achieving its aims, and which specifically tie in with research. These are Collaboration & Integration, Talent & Excellence Programs, and Spotless Reputation.

The committee studied this profile and strategy and discussed them with various stakeholders from the Princess Máxima Center, including staff members and management. It learned that the core area *Talent & Excellence Programs* reflects the Máxima's ambition to be world leading in the field of pediatric oncology: in order to belong to the best, talent must be attracted, trained and retained. On all levels, from PhD to (junior and senior) group leaders, the Máxima aims to offer a stimulating, safe and high-level working environment, while critically assessing performance and participation. The area *Spotless Reputation* covers not only the

scientific reputation of the Máxima, but also its more all-round trustworthiness towards all stakeholders, from researchers, charities, and financiers to parents and general public. The committee agrees that these focus areas for research are crucial for the Máxima's viability and long-term research quality; aspects of these will be discussed further on in this report.

The area *Collaboration & Integration* encompasses various kinds of internal as well as external collaboration and integration. One of these is collaboration and integration among Máxima researchers. At the Princess Máxima Center, a wide range of research is done, from fundamental cancer biology to clinical trials, and from translational precision medicine to psychological research into, e.g., pain reduction. The Máxima aims to stimulate inter- and multidisciplinary collaboration among these various fields and sub-fields. Further, the Princess Máxima Center intends to seamlessly bridge clinical care and research. The Máxima aims to be a comprehensive childhood cancer center (M4C) and to further develop synergistic interactions between care and research. Finally, collaboration and integration with external national and international partners is stimulated: locally, on the Utrecht Science Park with UMCU, UU, and the Hubrecht Institute; and also, globally with international top institutes. An affiliation with Hopp children's cancer center (KITZ) in Heidelberg has very recently been initiated.

Translation to structure and management

The strategic integrative and collaborative approach is currently being translated into the organizational structure and management of the Princess Máxima Center, with a strong focus on promoting the most complex integration: that of care and research. The M4C structure integrates the research branch of the organisation with the clinical departments Hemato-, Neuro-, Solid-Oncology, and Quality of Life. Within these M4C departments, specialized disease groups and themes are developed. Every disease group and theme is composed of multiple research groups as well as clinical representatives. M4C aims for a research organization that is as non-hierarchical as possible within the constraints of a research/care institute. As an example, at the time of the site visit the leadership of the disease groups was being redefined. Previously, they were chaired by a clinician, with a researcher as vice chair. Now, a research chair and a clinical chair are appointed as equals by the clinical directors of the various departments. Researchers are invited to join tumor board meetings; and the care and research sides meet in shared facilities and platforms such as the Trial and Data Center (TDC), Clinical Research Committee (CRC) and Biobank and Data Access Committee (BDAC).

A research directorate falling directly under the Princess Máxima Center's Board of directors is responsible for all research. In line with M4C and the integrative and collaborative strategy, a Strategic Research Board (SRB) was formed composed of the scientific and medical directors, research directorate, the four clinical directors, and representatives from the TDC, BDAC, and the pediatric oncology laboratory. In this manner, communication between the different departments with complementary strategic perspectives is guaranteed, resulting in an integrative approach in each decision and process concerning research.

The committee applauds the M4C approach, which it considers vital to attaining the goals and mission of the Princess Máxima Center. By integrating care and research throughout, from preclinical research to clinical practice, a continuous exchange is created from which both can greatly benefit. The committee noticed to its satisfaction that the vision behind M4C was shared by all members of the organization it met with during the site visit. The urgency of cooperating and creating synergy, particularly between care and research, is clearly felt at all levels of the Máxima. As a result, the committee noticed a strong sense of community.

During the interviews at the site visit, the committee and the representatives of the Máxima discussed the tensions that could arise from introducing a horizontal structure such as M4C within an organizational model

that traditionally has a vertical, hierarchical setup, i.e. a research institute or a hospital. It learned that the two models are allowed to co-exist. The familiar hierarchies are maintained where they are felt to be productive and necessary – in the case of research, to provide junior employees with a clear learning trajectory towards independent research and group leadership. The horizontal nature is sought in the juxtaposition of research groups, disease groups, themes, and departments, and in creating a level playing field for these elements to connect with one another. Conceived in this manner, the committee considers M4C to be of great value for the organization.

As a consideration for future development, the committee suggests that the focus on harmony in collaboration should not prevent the Máxima's researchers from adopting a critical attitude towards one another that is necessary for scientific improvement. It also points out that the Máxima's strategy and management are strongly growth oriented. This is natural for a young and dynamic organization with ambitious aims. Nonetheless, on a strategic level, the research department should start discussing where the current limits of its growth should lie. With the construction of two extra floors in its building, the limits of what the Máxima can handle in terms of research capacity, shared facilities and research groups are coming into view. The committee suggests defining the Princess Máxima's ideal size to define future policies (see also 'Viability') and considering upscaling of shared facilities when the institute grows.

Conclusion

The committee appreciates the Princess Máxima Center's mission of curing every child with cancer while maintaining optimal quality of life, as well as the key objectives and focus areas designated to work towards achieving this mission. The committee finds that the Center is a unique national care and research facility answering to an urgently felt need. It applauds the integrative M4C approach aimed at synergistic interactions between care and research, which it considers vital to attaining the goals and mission of the Princess Máxima Center. As a consideration for future development, the committee suggests that the focus on harmony in collaboration should not prevent the Máxima's researchers from adopting a critical attitude towards one another that is necessary for scientific improvement. On a strategic level, the research department should start discussing where the current limits of its growth should lie.

5.3 Research Quality

Achievements and recognition

As mentioned above, research at the Princess Máxima Center is closely connected to clinical care. Most research groups are therefore linked to the four pillars of hemato-oncology (HO), neuro-oncology (NO), solid oncology (SO), or quality of life (QoL), although Principal Investigators (PIs) are granted academic freedom and are not limited to M4C. As a result, some of the 36 research groups fall outside the M4C structure, which is allowed.

The committee talked to representatives of the various pillars and research groups. It also looked at evidence regarding grants, publications, and other forms of external recognition of research at the Princess Máxima Center. It found that in its brief period of existence, research at the Princess Máxima Center has increased strongly in line with the Máxima's growth. The number of scientific publications has grown from 120 at the start in 2016 to 474 in 2020 (with 2021 promising continuation of growth, as this number had already been surpassed at the time of the site visit), reflecting recent staff increase.

Over the past period, the Máxima gained 3 ERC Starting, 1 Consolidator and 1 Advanced grants; 6 NWO personal grants (Veni, Vidi, Vici); 11 European grants, including an ITN/Marie Skłodowska-Curie Actions Horizon 2020 grant for the VAGABOND platform; and international and national competitive awards, such as

the Keio Medical Science Prize, the Deutsche Krebshilfe Preis, the St. Baldrick's Innovation Award, the AACR St. Baldrick's career development award and the ZonMw Open Science Impuls. The Princess Máxima Center participates in or leads various EU-funded projects.

The various groups and researchers participate in relevant national and international research networks, guideline committees and consortia, in line with the Máxima's internationalization strategy. The Princess Máxima Center research management is aware that in such collaborations, its unique position and exceptional size (particularly in Europe) should not lead to a dominant position; instead, it aims at collaboration and integration, letting all participants contribute equally departing from their own expertise. The collaboration with Hopp KITZ in Heidelberg is undertaken as an extra impulse towards joint development of research programs, grant applications, and research as well as clinical infrastructure, and is considered to be a valuable addition to the solid ties between the Princess Máxima Center and the Utrecht Science Park, including UMCU, Hubrecht Institute, and WKZ.

The committee finds that in the few years that the Máxima has been operational, it has managed to set a high scientific standard and to recruit top scientists. Its researchers have made strong contributions to science, such as the field of tumor evolution, mutational causes and mechanisms, organoid tumor models, imaging, drug screens and delivery, treatment toxicity and late effects of treatment, where the Dutch LATER cohort (all pediatric cancer survivors from 1963 onwards) forms a unique data source. Exceptionally strong programs also include the leukemia program addressing the whole translational value chain from basic and translational research to clinical trial development (i.e. the international multicenter trials *ALLtogether1* and *HaemSMART*) and the solid tumor program with the iTHER2.0 precision medicine program and the advancement of RNAseq-based molecular diagnostics. Further, the Princess Máxima Center has laid the groundwork to be leading European Center in CNS directed delivery strategies for brain tumor patients with key strategic investments. The committee concludes that research at the Princess Máxima Center can be considered excellent, which is quite an achievement in such a brief time span.

Research facilities, research integrity and open science

The Princess Máxima Center has a number of core facilities to support and stimulate research and clinic, as well as the integration of the two. One of these is the Trial and Data Center (TDC), which plays a central role at the Máxima. It encompasses over 85 FTE in personnel including data managers, trial managers, research nurses and a statistical services group. The TDC is responsible for facilitating the large number of clinical trials being run by or at the Máxima, with the result that almost every patient participates in several (inter)national trials or studies. The Máxima also has a central biobank of pediatric malignancies. The primary objective is to develop a collection of tumor and healthy material, and clinical, genetic and biological data during the diagnostic phase, during treatment and long-term follow-up. This includes biomaterials and data of all children with suspected and diagnosed malignant disease (and related) at the institute, who have signed the informed consent form of the Biobank and Data Access Committee (BDAC). Primary datasets are shared through the publicly available data resources through or with support of the Big Data Core, as one of the created in-house facilities. Finally, a diagnostics lab coordinates the distribution and availability of test samples and data upon approval from the BDAC.

The committee appreciates the research facilities in place at the Máxima and the way they contribute to M4C and open science. It learned that the TDC plays a pivotal role in the Princess Máxima Center, also as a hub connecting research to care. The diagnostics lab also enables encounters between the two. The Big Data Core takes up many important tasks related to data handling and storage, adherence to the FAIR principles, and bioinformatics analysis and support. The Biobank is a very powerful resource that will only grow in importance. The committee finds that as a new center, the Máxima has the opportunity to build an optimal

data structure and big data facility and can set the standard for the future. Many aspects are still work in progress, but the Máxima is prioritizing creating the best possible structure. It could consider looking into other channels than the Biobank to promote data sharing. It should also consider carefully which facilities to create internally, and where to make use of systems in place elsewhere, as is currently already done regarding animal facilities, organoid growth, and single cell genomics at Utrecht Science Park.

Other ways to promote scientific integrity and open access are summarised in the Princess Máxima Center's aim to uphold a Spotless Reputation. It aims at transparency towards stakeholders and funding partners, and at clear and open communication towards the public. According to the committee, the Máxima is clearly committed to its high moral and scientific standards in openness, transparency, and integrity. It would suggest replacing the term 'spotless' with an alternative such as 'excellent', to indicate that openness and transparency also include the room to make mistakes, openly communicate about them and show they are properly dealt with.

Future developments

According to the 2020-2024 strategy, an extra focus on immunotherapy and neuro-oncology is foreseen. These fields have been selected because developments here are felt to have the greatest impact on achieving the mission of curing all children with cancer. Neuro-oncology is the field with the smallest survival rates, and immunotherapy is considered a promising research direction due to recent success in adult oncology, combined with the use of CAR-T cell therapy in hematological malignancies and antibody treatment in neuroblastoma.

The Máxima is investing in neuro-oncology through its relation with KiTZ in Heidelberg, since their fundamental pediatric neuro- oncological research program supplements the Máxima's advanced translational expertise. In the future, it will be important to shape an own internationally visible research program based on this advanced translational expertise, which will ideally be complementary to the research priorities in Heidelberg. The Máxima has also invested in the preclinical brain tumor program, by preparing for a neuro-immune-oncology program. Research groups focusing on the generation of brain organoids to study pediatric brain tumors have started. The Máxima also invests in the construction of a neurosurgery suite. For this advanced, state-of-the-art operation room, the Cirq robot arm of Brainlab was purchased and implemented to optimize tumor biopsies and potentially drug delivery at later stage in children with brain tumors. Furthermore, an interoperative MRI is being purchased. Also, the infrastructure to start focused ultrasound (FUS) collaboration with the UMCU is being set up, to advance research into drug delivery.

For immunotherapy, a translational principal investigator was recruited to set up an immune-monitoring platform, including a liquid biopsy protocol in collaboration with others. The Máxima intends to build a Cell Therapy Facility to start their own CAR-T cell research programs. The automated cell processing machine 'Prodigy' of Miltenyi was recently purchased, thanks to a donation, and will be used for a humanized CD19 CAR-T cell product for ALL and lymphoma. Also, a renowned expert in the field of immune-oncological fundamental research is being recruited. In addition, it was mentioned that space will be dedicated in the newly to build floors to accommodate these immune oncology procedures.

The committee appreciates these initiatives and applauds the acquisition of equipment in order to boost research in these areas. It feels that the current investment in these two fields could be made more effective and productive if they were focused more. The Princess Máxima Center could finetune its aims and strategy regarding these fields, for instance through a more precise recruitment policy where the expertise of researchers it aims to attract is specified. In the future, it will be important to (i) complement fundamental

research expertise with manufacturing expertise (GMP) in this field; (ii) join European networks focussing on cellular therapies for (pediatric) cancer patients and (iii) potentially establish bilateral synergistic industry cooperations.

Another strategic aim of the Princess Máxima Center is to boost Quality of Life research. The committee supports the Máxima in this. As mentioned before, the committee is impressed with the research groups involved here. While the QoL researchers are well-supported by the TDC, they could be better connected to the big data infrastructure. Their PROM (patient-reported outcome measure) surveys should be linked to all trials as standard procedure. The committee also recommends looking for more opportunities to connect QoL with basic research, for instance in the study of toxicity. In this way, QoL gains even more prominence, in line with strategic targets. According to the committee, it is also worth formulating a clear strategy on the development of this group and considering whether more hires are needed, for instance in intervention research.

Conclusion

The committee concludes that research at the Princess Máxima Center can be considered excellent. It appreciates the research facilities in place at the Máxima and the way they contribute to M4C and open science. Many aspects surrounding the data structure are still work in progress, but the Máxima is prioritizing creating the best possible structure. It could consider looking into other channels than the Biobank to promote data sharing, and should consider carefully which facilities to create internally, and where to make use of systems in place elsewhere. According to the committee, the Máxima is clearly committed to its high moral and scientific standards in openness, transparency, and integrity, as the focus on ‘spotless reputation’ signifies. It would suggest replacing the term ‘spotless’ with an alternative such as ‘excellent’, to indicate that openness and transparency also include room to make mistakes. The committee appreciates the current strategic investment in the areas of immunotherapy and neuro-oncology, and suggests further focusing this effort for maximum effectiveness. The committee also recommends looking for more opportunities to connect Quality of Life with basic research and formulating a clear strategy on the development of this group.

5.4 Societal Relevance

Valorization, relevance and outreach

Due to its focus on curing every child with cancer while maintaining optimal quality of life, societal relevance of the research done at the Princess Máxima Center is evident. The Máxima was founded with the purpose of boosting pediatric oncology in the Netherlands and is clearly fulfilling its purpose. The translation of research output to the clinic is greatly facilitated by the integrative M4C approach, and by the presence of dedicated support staff and facilities, e.g. the Knowledge Transfer Office and communications department. Recently, a patent portfolio with four filed patents has been developed. With the recruitment of a business developer in 2021, the Máxima aims to recognize valorization opportunities even better. In addition, an Intellectual Property policy has been developed. This policy offers a framework to protect and commercialize knowledge and intellectual property, and participation of employees in spin-off companies. It aims to encourage the incorporation of knowledge valorization and exploitation in every researcher’s daily business.

Societal relevance of the Princess Máxima Center is also enhanced through its many outreach activities. Among these are events for patients and parents/guardians, participation in the Dutch National Science Weekend, the Expedition Next event organized by the National Science Agenda, the Tom Voûte young

investigator awards organized by KiKa, presentations at the UU Studium Generale, primary schools etc. Princess Máxima Center researchers frequently appear in national and international media.

Finally, the Princess Máxima Center contributes to academic education. Researchers at the Máxima are closely connected to Utrecht University (UU), often through the UMCU. The Máxima currently supervises 162 PhD students (including MD PhD candidates) and 73 Master students, of whom the majority is affiliated with the UU. In addition to contributing to academic education as offered by the UU, the Princess Máxima Center also organizes specific courses through the Máxima Academy, where its educational and training activities are organized. An example is the frequently offered Data Management and Research IDT course. The Princess Máxima Center has also organized a summer school course on childhood cancer, which was attended by some 30 participants from all around the world and received an overall evaluation score of 9.1/10. A summer school connected to the EU consortium VAGABOND was held as well.

A future direction might be investing more in the teaching-research nexus and expanding educational activities to enhance the dynamic exchange with UU, UMCU and other possible partners, for instance by coordinating and contributing to GSLS Master and PhD courses, and to ensure embedding of the Maxima PhD students in the Utrecht Science Park.

Conclusion

The committee concludes that societal relevance of the Princess Máxima Center is excellent. The Máxima was founded with the purpose of boosting pediatric oncology in the Netherlands and is clearly fulfilling its purpose. The many outreach activities enhance this relevance. A future direction towards enhancing societal relevance might be strengthening the teaching-research nexus through a dynamic exchange with partners such as UU and UMCU.

5.5 Viability

Financial health

The financial structure of the Princess Máxima Center is unique due to the contribution of KiKa, which was involved in the original initiative of starting the Máxima. This charity contributed to the financing of the building itself, through a direct payment of € 48,5 million for the research part of the €180 million building. KiKa also contributes €10 million a year as core research funding. Furthermore, the Dutch Ministry of Health, Welfare and Sport (VWS) contributes 'Availability Contribution Academic Healthcare' (BBAZ), which constituted €10 million in 2020 and a projected €11 million in 2021. Finally, research is funded through project funding by KWF, NWO, KiKa, the Máxima Foundation, and others. In 2021, this was projected to amount to €19 million, adding up to a total of €40 million in research funding. The committee considers this a very good funding situation.

The committee learned that the VWS BBAZ funding started with a 3-year project and needs to be renegotiated. The Princess Máxima Center aims to make it a structural part of research financing and to increase it. Similarly, the management hopes to receive additional KiKa core funding as well. The committee supports this considering the Máxima's unique position and its great added value in promoting pediatric cancer research and its translation into clinical practice. It considers structural and sufficient funding necessary to advance towards the aims set by the Princess Máxima Center. The impressive growth and achieved quality warrant such structural investments.

The committee feels that more could be done to repay parents for their essential role in enabling and stimulating research. The committee learnt from its conversation with parents' representatives that they

spend considerable time and effort on participation in the Máxima's research. They connect with the Máxima on many levels, from research grants and international collaborations to legal and ethical issues. However, patient/parent representatives struggle to follow the more technical and scientific content concerning basic science, grant proposals, or the Biobank, and would like to receive support or education here. The committee also learned that they usually serve the Princess Máxima Center on a voluntary basis. The committee recommends creating a stronger support system for the parent/patient representatives involved, and to compensate them for the considerable time and effort they put into the Máxima and its research.

HR: PhD policy and training

According to its profile and strategy, the Princess Máxima Center aims to be world leading in the field of pediatric oncology and therefore to attract, train and retain research talent. On all levels, from PhD to (junior and senior) group leaders, the Máxima strives to offer a stimulating, safe, pleasant, and high-level working environment, while being critical on performance and participation.

Currently, the Máxima trains more than 160 PhD students originating from 33 different countries. All PhD students who spend most of their time at the Máxima are enrolled in one of the campus PhD programs. This allows the Máxima to tap into the extensive and expert PhD education and supervision system that is present at the UMC Utrecht and Utrecht University. Many of the PhD students are therefore enrolled in the Graduate School of Life Sciences (GSLs) of the UU. This graduate school encompasses over 1500 PhD students enrolled in 15 different PhD programs. The graduate school and its programs offer a wide variety of courses, ranging from cellular biology, statistics or epigenetics to soft skills courses such as time-management, presentation and writing skills. A research integrity course was recently introduced as an obligatory course for PhD students of the GSLs. Most PhD programs organize an introduction and an annual retreat. PhD students who do not enter the GSLs enrol in equivalent graduate schools at other universities.

The Máxima takes GSLs guidelines on PhD supervision as its standards. These include formation of a supervisory committee with external members who meet annually with the PhD student and the direct supervisors to review the progress and guidance of the PhD track. The meeting of the supervisory committee takes place in addition to the annual interview held between PhD student and direct supervisor(s) at the Máxima and is to be organized by the PhD students themselves. The PhD candidate can also turn to members of this committee when problems in supervision arise. New PhD supervisors are encouraged to take courses in PhD supervision offered by the Graduate School and all currently starting PhDs should have at least two supervisors.

The PhD students in the Máxima have come together in the PriMa PhD group. This self-organized group of PhD students gets together during lunches, meetings, and other social gatherings. They organize small workshops and seminars on topics they want to know more about, such as research communication and mental health. They have also established a buddy system pairing every new PhD student to a third- or fourth-year PhD student. The PriMa PhD group is financially supported by the Máxima with a budget for the organization of such events. In addition, the structure is specifically and actively supported by one of the staff members.

The committee met with PhD students during the site visit and learned that they were all satisfied with their positions and the guidance and supervision they receive. The COVID-19 period prohibited social meetings and made the integration of new PhD students more difficult, in particular for students from abroad. PhD students were not always completely informed about educational and supervision options, especially outside the Máxima. The committee learned that the provisions in place for the PhD community have since improved and that much effort is put into PhD student support and guidance. However, PhD students and at

the Maxima have not been granted any COVID-19 extensions, even though their research and work must have been affected by it. The committee suggests recommends looking into the delays PhDs suffered and considering extensions here.

HR and talent management

Postdoctoral researchers at the Princess Maxima Center are usually hired for a period of four years. They are supported in various ways, and have created their own peer review system. Another concrete step in supporting postdocs has been the recent formulation of a concise policy and uniform procedure regarding the granting of permanent contracts for postdocs (although the postdocs interviewed by the committee had not yet been made aware of this). Maxima postdocs have also set up their own postdoc platform that provides a buddy system, organizes events and informal contact moments with the Board of Directors, and discusses those issues particular to their career stage. Due to the coronavirus pandemic, the activities of the platform have quietened down to an extent. To reinvigorate the postdoc platform, a group leader has been asked to actively support the platform and to help develop new initiatives, supported by Human Resources (HR) and the research management.

According to the self-evaluation of the Maxima, postdocs typically struggle with such issues as the constant pressure to deliver excellent research output, job and/or career insecurity, as well as expectations of independence whilst at the same time being dependent on a supervisor. Such issues are faced at a period when many are also starting families, and the COVID-19 pandemic added to many of these insecurities. Despite the support lent to postdocs, the committee found that these insecurities are strongly felt by the postdocs it met with. It recommends offering them better career development opportunities by creating transparent policies for contract extensions, tenure track positions, and guidance towards alternative career tracks, in order to be able to also attract international research talent. The committee also points out that postdocs, like PhD students, should receive contract extensions when their research was affected by COVID-19.

The committee noticed that tenure track early and mid-career researchers could also be provided with more stability and security. Tenure trackers often come from a background other than pediatric oncology and enter into a field that is new to them and highly specialized. As a result, they take a risk in entering into this field. As group leaders, they typically follow a 5-year research track with a halfway midterm evaluation. The committee learnt that they consider this a very limited time to establish a research group and make it productive. Also, the tenure track evaluation procedure is unclear to them and to the committee, including the criteria and the moments at which they are evaluated. This creates uncertainty and stress. The committee recommends offering these researchers more time to prove their worth, by extending their contracts to 7 years, with the evaluation for tenure taking place 5 years after starting their independent group. It appreciates the adaptation of evaluation procedures and criteria undertaken by the HR department and recommends providing transparency and clarity to all.

Junior and mid-career researchers are provided with support through a peer review and support system, and recently, a leadership program was developed based on their needs and wishes. Furthermore, all junior group leaders are connected to a senior group leader as mentor. A selection of junior group leaders started a peer intervention group under active guidance from HR. New group leaders are strongly encouraged to participate in the group leader course when they start at the Maxima. The committee learned that these options were appreciated by junior and mid-career staff. For running their groups, PIs receive a yearly bench fee (excluding their salaries) of €150 thousand for junior and €200 thousand for senior group leaders. This can be used for attracting PhDs or postdocs. They also enjoy the academic freedom to do research outside

the M4C structure, especially in the case of preclinical research. The committee appreciates this clear and attractive setup.

Academic culture and diversity

As mentioned earlier, the Princess Máxima Center strives for a flat and non-hierarchical, open research environment where collaboration and integration are stimulated. This philosophy is visible in the design of the building, where researchers meet one another and clinical staff in coffee corners and shared facilities. The Máxima organizes regular research retreats and seminars, taking care to also include PhD students. Newsletters, guest lectures or informal gatherings all work towards eliminating boundaries and stimulating group culture. The committee encountered a community that had strong ties in spite of the COVID 19-period reducing social interaction, and where everybody was mission-aligned.

The Máxima's non-hierarchical M4C approach incorporates existing hierarchies. The committee noticed that certain habitual approaches stemming from these more traditional structures are still visible. It noticed for instance that the HR approach is very leadership oriented. Also, while research staff is very diverse with a good gender balance, the key positions are predominantly occupied by male staff members. The panel learned that diversity and inclusion are on the agenda of the Princess Máxima Center, where a diversity and inclusion working group and a gender equality sub-group have been set up. A gender equality plan 2021-2025 for the Máxima is currently in development, and an internal Women in Science initiative has female leaders reflect on their challenges together. The committee appreciates these efforts but points out that they have limited reach in the organization in their current form. The Princess Máxima Center should invest in sensitivity trainings for all employees to raise awareness of underlying mechanisms and unconscious biases that form barriers to female researchers and/or other minority groups.

A good example of raising awareness in this manner is the Máxima International Community (MIC). The MIC team was first established in response to challenges with on-boarding, relocation, and assimilation processes among researchers coming from outside the Netherlands and has since branched out to all employees. Its three main goals are to create a community for the international employees, to be a point of contact for international affairs and help improve current services or processes, and to create awareness about international and intercultural needs within the whole organization. The MIC team initiates social interactions, offers a buddy system, and helps with problems international employees encounter. It also tries to remove language and culture barriers and to improve bilingual communication, for instance on the website, intranet, email, staff meetings, and signage in common areas. MIC also aims to improve awareness of cultural issues within the whole organization by providing good access to knowledge and information, through organizing events where all staff are involved, diversity days, or the implementation of a new, bilingual, intranet. The committee understood from staff members and PhD students that the initiative has made quite a difference and improved the integration of international staff into the Princess Máxima Center's community. It finds that continuation of this initiative needs attention under the current COVID-19 circumstances.

Future developments

Provided that the financial situation is improved as explained above and stabilized, the Princess Máxima Center can continue developing. Its building will shortly be completed with a sixth and seventh floor, but there is potential for much more growth. The committee points out that the time has come to take a step back and channel this growth by choosing where the Princess Máxima Center wants to excel and where it prefers to bring in external parties and make use of their expertise. This can be done not only by establishing collaborations such as that with KITZ in Heidelberg, but also by determining the Center's position within the Netherlands relating to clinical as well as fundamental research. The committee also recommends looking

for further connections to adult oncology. The Princess Máxima Center should avoid isolation, welcoming others and making sure to stay up to date when it comes to developments outside its own specialism.

Conclusion

The committee considers the current funding situation to be very good. It considers structural and increased VWS BBAZ and KiKa funding due to the Princess Máxima Center's unique position and its great added value in promoting pediatric cancer research and its translation into clinical practice. It recommends creating a stronger support system and compensation for the parent/patient representatives involved.

The Princess Máxima Center places emphasis on attracting and retaining research talent through academic culture and HR policy as key to its future viability. The committee approves and was pleased to encounter an open, tight-knit and mission-aligned community. It appreciates PhD policy and training; in line with this, it recommends offering postdocs better career development opportunities through creating transparent HR policies for contract extensions, tenure track positions, and guidance towards alternative career tracks. Postdocs and PhD students should also receive contract extensions when their research was affected by COVID-19. The committee found that tenure track early and mid-career researchers benefit from the financial and academic freedom they enjoy as well as from the training and assistance they receive in order to establish and run their research groups. However, it points out that they could be provided with more stability and security by giving them more time to prove their worth through contract extension. The committee appreciates efforts to promote diversity and recommends investing in sensitivity trainings for all employees.

To further promote viability, the committee recommends channelling the Máxima's growth by establishing where the Princess Máxima Center wants to excel and where it prefers to bring in external parties and make use of their expertise, for instance in adult oncology, abroad, or in the Netherlands. It considers structural and sufficient funding necessary to advance towards the aims set by the Princess Máxima Center. The impressive growth and achieved quality warrant such structural investments.

Appendix 1: The SEP 2021-2027 Criteria and Categories

The committee was requested to assess the quality of research conducted by the UHS as well as to offer recommendations in order to improve the quality of research and the strategy of the UHS. The committee was requested to carry out the assessment according to the guidelines specified in the Strategy Evaluation Protocol. The evaluation included a backward-looking and a forward-looking component. Specifically, the committee was asked to judge the performance of the unit on the main assessment criteria and offer its written conclusions as well as recommendations based on considerations and arguments. The main assessment criteria are:

- 1) **Research Quality:** the quality of the unit's research over the past six-year period is assessed in its international, national or – where appropriate – regional context. The assessment committee does so by assessing a research unit in light of its own aims and strategy. Central in this assessment are the contributions to the body of scientific knowledge. The assessment committee reflects on the quality and scientific relevance of the research. Moreover, the academic reputation and leadership within the field is assessed. The committee's assessment is grounded in a narrative argument and supported by evidence of the scientific achievements of the unit in the context of the national or international research field, as appropriate to the specific claims made in the narrative.
- 2) **Societal Relevance:** the societal relevance of the unit's research in terms of impact, public engagement and uptake of the unit's research is assessed in economic, social, cultural, educational or any other terms that may be relevant. Societal impact may often take longer to become apparent. Societal impact that became evident in the past six years may therefore well be due to research done by the unit long before. The assessment committee reflects on societal relevance by assessing a research unit's accomplishments in light of its own aims and strategy. The assessment committee also reflects, where applicable, on the teaching-research nexus. The assessment is grounded in a narrative argument that describes the key research findings and their implications, while it also includes evidence for the societal relevance in terms of impact and engagement of the research unit.
- 3) **Viability of the Unit:** the extent to which the research unit's goals for the coming six-year period remain scientifically and societally relevant is assessed. It is also assessed whether its aims and strategy as well as the foresight of its leadership and its overall management are optimal to attain these goals. Finally, it is assessed whether the plans and resources are adequate to implement this strategy. The assessment committee also reflects on the viability of the research unit in relation to the expected developments in the field and societal developments as well as on the wider institutional context of the research unit

During the evaluation of these criteria, the assessment committee was asked to incorporate four specific aspects. These aspects were included, as they are becoming increasingly important in the current scientific context and help to shape the past as well as future quality of the research unit. These four aspects relate to how the unit organises and actually performs its research, how it is composed in terms of leadership and personnel, and how the unit is being run on a daily basis. These aspects are as follows:

- 4) **Open Science:** availability of research output, reuse of data, involvement of societal stakeholders;
- 5) **PhD Policy and Training:** supervision and instruction of PhD candidates;
- 6) **Academic Culture:** openness, (social) safety and inclusivity; and research integrity;
- 7) **Human Resources Policy:** diversity and talent management.

Appendix 2: Programme of the site visit

2 November 2021

Introduction

18.30 Dinner

3 November 2021

Welcome

09.00 – 09.15 Welcome
09.15 -10.00 Tour - care departments & research facilities
10.00 – 11.00 Introduction by RvB, Research Board & Management
11.00 -11.30 Coffee break / discussion time

M4C Focus areas

11.30 -12.15 Hemato - oncology Disease Group: Lymphoma
12.15 -13.00 Solid tumors Disease Group: Renal tumors
13.00 -14.00 Lunch / discussion time
14.00 - 14.45 Neuro - oncology Disease Group: Embryonal & rare CNS tumors
14.45 -15.30 Quality of Life Theme: Neuropsychology
15.30 -16.00 Tea break / discussion time

Talent program

16.00 - 16.10 Graduate school & programmes
16.10 - 16.30 PhD students
16.30 - 16.50 Postdocs
16.50 - 17.10 Early career Principal Investigator
17.10 - 17.30 Mid career Principal Investigator
17.30 - 17.50 Senior Principal Investigator
17.50 - 18.00 Closure
18.30 Dinner

4 November 2021

Supportive structure(s)

8.30 - 9.00 Human Resources
9.00 - 9.30 Public Outreach
9.30 - 10.00 Financial support

10.00 - 10.30 Coffee break / discussion time

Research & Infrastructure

10.30 - 12.00 Diagnostics; Biobank; Big Data Core; Trial and Data Center

Non-academic stakeholders

12.00 - 12.15 Client council & VKN (Childhood Cancer Association Netherlands)

Long term ambitions

12.15 - 12.45

Research Management

Closing

12.45 - 14.15

Lunch & discussion

14.15 - 15.00

Presentation first impression

15.00 - 16.00

Drinks

Appendix 3: Quantitative data

The following quantitative data on the research unit's composition and funding have been included in this report according to the requirements stated in Appendix I of the SEP 2021-2027.

Table 1: Overview of research staff over the years

| | 2016 | | 2017 | | 2018 | | 2019 | | 2020 | |
|------------------------|-----------|-------------|------------|------------|------------|------------|------------|------------|------------|------------|
| Research groups | 14 | | 19 | | 26 | | 28 | | 35 | |
| Group leaders | | | | | | | | | | |
| | # | fte | # | fte | # | fte | # | fte | # | fte |
| Scientist | 16 | 12,4 | 28 | 22,6 | 72 | 66,8 | 97 | 89,3 | 121 | 11,3 |
| PhD Candidate | 13 | 12,5 | 30 | 36 | 80 | 56,1 | 96 | 95,4 | 124 | 122,6 |
| MD PhD Candidate | 3 | 3,0 | 8 | 7,8 | 16 | 15,2 | 26 | 24,7 | 38 | 37,1 |
| Technician | 10 | 9,5 | 17 | 16,2 | 32 | 30,8 | 47 | 45,3 | 56 | 54,6 |
| TDC | 3 | 2,6 | 22 | 18,4 | 50 | 43,8 | 63 | 54,0 | 99 | 85,5 |
| Staff | 4 | 3,2 | 4 | 2,5 | 9 | 7,8 | 17 | 12,5 | 20 | 15,1 |
| Total | 59 | 51,5 | 123 | 109 | 257 | 238 | 371 | 343 | 486 | 450 |
| Students | 4 | | 21 | | 52 | | 56 | | 73 | |
| Associate professors** | 2 | | 4 | | 4 | | 4 | | 4 | |
| Full professors** | 8 | | 10 | | 14 | | 17 | | 21 | |

Reference dates (December 31 of each year) were used to collect data for this table.

*A margin of error should be anticipated since some staff divide their time between care and research tasks.

Dependent on this division they are counted as either research or care personnel.

**Máxima paid employees (Research and Care) with an appointment at any (Dutch and abroad) University as associate or full professor

Table 4: The number of PhD candidates that have been appointed in the Máxima since the beginning up to 2020

| Starting year | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | total |
|---------------------------|------------|-------------|-------------|-------------|-------------|--------------|------------|
| Total | 5 | 33 | 29 | 29 | 54 | 37 | 187 |
| Grad in year 4 or earlier | 1 20% | 6 18,2% | 2 6,9% | - | - | - | 9 |
| Grad in year 5 or earlier | 4 80,0% | 3 9,1% | - | - | - | - | 7 |
| Grad in year 6 or earlier | - | - | - | - | - | - | - |
| Not yet finished | - | 23 69,7% | 25 86,2% | 26 89,7% | 49 90,7% | 37 100,0% | 160 |
| Discontinued | - | 1 3,0% | 2 6,9% | 3 10,3% | 5 9,3% | 0 | 11 |

It should be noted that the numbers are an indication. Many PhD candidates started their PhD project in a different institute and followed their supervisor to the Máxima center at some point during the project. This initial multiple institute structure complicates an exact representation. Nevertheless, the number of PhD students and the success rates give a good reflection of the starting years.

Table 6: Scientific output

| | 2016 | 2017 | 2018 | 2019 | 2020 |
|-----------------------------------|------|------|------|------|------|
| Number of Publications | 120 | 170 | 228 | 332 | 474 |
| Filed Patents | - | - | - | 1 | 3 |
| Number of graduated PhD students* | - | 3 | - | 2 | 3 |
| Awards and prizes | 3 | 10 | 11 | 17 | 14 |
| Veni/Vidi/Vici | 1 | 2 | 1 | - | 2 |
| ERC | 1 | 1 | - | 2 | 1 |
| EU grants (excl. ERC) | 1 | - | 2 | 4 | 4 |
| Oncode memberships | - | 2 | 4 | - | - |

*Number is related to the transition of the group leader from the former institute to the Princess Máxima Center