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1. Executive Summary

The IRC was given excellent documentation concerning the activities of the various Investigators and the overall goals of the organization. Other questions were readily answered as they arose. It is clear that this review is performed early in the life of Oncode, and thus it is hard to measure progress towards the high-level goals. On the other hand, this was an excellent time to review whether the structure established is indeed appropriate, if the leadership and management teams are effective, and if the researchers embrace the important goals and spirit of this institute. With respect to all three issues, Oncode has been extremely successful. As detailed below, Oncode has created a structure within which synergy between more fundamental cancer research and the translation of those discoveries can flourish. It is clear that the allocation of “non-earmarked funds”, i.e. base funding that enables high-risk studies, opens the door for rapid testing and implementation of new leads for cancer diagnostics, prevention and treatment, and fills a gap in the Dutch funding landscape. All too often in the past, it seems that exciting but risky research avenues were dropped, because they did not fit the goals for which funding was awarded. Many OI investigators indicated that beyond the Oncode funds, they do not have money to spend flexibly to pursue unexpected or novel findings. As this latter drives innovation, the investment is well spent.

Among the specific achievements of Oncode we note:
- Oncode’s outstanding, proactive efforts in “valorization”, which aim to transfer discoveries as quickly as possible into spinoff companies and collaborations with larger companies. This is also reflected in the way they encourage young scientists to think about the impact their work can have on patients and the wider Dutch landscape.
- Noteworthy as well is the successful enlargement of the Oncode community, achieved both by adding clinical collaborations and a second set of Investigators of more diverse specialties (chemistry, computation, modelling).
- Third, we praise the sponsoring of retreats, cancer-specific meetings, and opportunities for cross-feeding between clinicians and scientists who had never collaborated before. The creation of new and highly fruitful collaborations will pay off in the second phase of funding.
- Finally, we sense the existence of true commitment to Oncode’s goals extending from postdocs and students to the Advisory board. This is a significant achievement for an organization that has existed less than 3 years.

Key suggestions:

Prioritization: The Oncode program is very full, with many activities, and this impression likely reflects the process of setting up the network. It will be important to increase the level of focus, and clarify messaging around the topics where Oncode will have the most impact.

Clinical studies: The Oncode Institute should review its Clinical study advisory board and clarify how much funding is available for Clinical Proof of Concept trials and further POC research.

Mode of Funding: It is very important that the Oncode funding is centralized and awarded to the network as a whole to achieve long-term goals, even if the funding enables bottom-up discovery research. A collaborative initiative like Oncode requires long-term vision that is not locked into the short-term deliverables that are characteristic of competitive calls.
2. Review process

2.1 Introduction

Within Oncode’s Strategic plan, an assessment process was planned to evaluate Oncode’s phase I performance and its phase II (2023-2027) strategic plan, resulting in renewed funding. An independent International Review Committee (IRC) consisting of national and international renowned experts, will perform the review. In November 2020 the IRC will review Oncode on an institutional level, assessing its phase I performance and its progress in achieving its strategic objectives, described in the strategic plan and further detailed in its KPAs. This first review enables Oncode’s funders to make timely financial preparations for a second phase resulting in phase II budget reservations by Oncode’s funders. A second review in late 2021 / early 2022 will focus on Oncode’s phase II strategy and the envisioned research team for phase II. In accordance with Oncode’s strategic plan phase I will seamlessly roll over into phase II in September 2022.

2.2 Role and assignment of the International Review Committee

The IRC has been tasked with performing an assessment of Oncode’s progression towards its strategic goals as formulated in the strategic plan and further detailed in its six KPAs. Specifically, the IRC has been asked to assess whether Oncode’s scientific strategy is being implemented effectively to optimally utilize the scientific and translational potential of the Oncode community. In addition, the IRC has been asked to assess the added value of the Institute – i.e., to what extent the combined and integrated activities of the Institute have created (or are in the process of creating) an internationally unique research environment. As part of the assessment, the IRC has also evaluated if the Institute has implemented the proper tools and processes to manage its activities in order to achieve its strategic goals.

Through this evaluation report the IRC presents Oncode’s MB and its funders with a comprehensive overview of its assessment of the institute. This report summarizes the findings, conclusions and recommendations of the IRC on the basis of the written and oral information provided by Oncode. For Oncode’s funders, the Assessment Report will serve as a basis for making a balanced decision on funding Oncode for a second 5-year term.

2.3 Composition of International Review Committee

The IRC consisted of:

Prof. Susan Gasser PhD (Chair), Director emeritus Friedrich Miescher Institute
Prof. Josep Tabernero MD PhD, Medical Oncologist, Head of Medical Oncology at Vall d’Hebron University Hospital and Director at Vall d’Hebron Institute of Oncology (VHIO)
Prof. Liesbeth de Vries MD PhD, Medical Oncologist, Department of Medical Oncology UMCG
Prof. Richard Marais PhD, Director of the CRUK Manchester Institute & Oncode International Advisory Board member
Derek Waddell, Founder & CEO of 8iC Limited
Prof. Ivan Dikic, MD PhD, Director Institute of Biochemistry II, Goethe University Frankfurt
Dr. Tim Wells, CSO Medicines for Malaria Ventures & Non-Executive Director at Kymab Ltd.
2.4 Data provided to the committee

The IRC has received a summarizing report by the Management board of Oncode, the report was accompanied by the following documents:

- Strategic plan phase I
- Terms of reference IRC
- Good governance charter
- Overview of funding & expenditures
- Annual report 2018 & 2019 (Including the Individual OI progress reports)
- Advice IAB – Annual report 2018 & 2019
- Metric report, including the annual updates
- Overview Clinical activities

2.5 Agenda of the meeting

During a 2-day site visit, the IRC has been able to assess Oncode’s performance through interviews and discussions with various stakeholders. Oncode’s MB has ensured that all relevant topics are represented during the site visit, enabling the IRC to assess the quality of Oncode’s performance in the various KPAs. The meeting has been organized according to the wishes of the IRC. A detailed agenda can be found in appendix I. The agenda included presentations and discussions with the Managing Board and relevant stakeholders, namely:

- Representatives of the Research Management Committee
- Representatives of the Clinical Advisory Board
- Representatives of the Supervisory Board
- A selection of Oncode Investigators (16) and Oncode researchers (6)
- Representatives from Oncode’s funders
- Deans of Oncode’s partner institutes
- Oncode business developers

2.6 Judgement of the IRC

The evaluation of the institutes six KPA’s constitutes the core of the assessment. The qualitative assessments of each KPA is supplemented by assigning each KPA one of the following scoring categories:

**Exceptional** → The institutes performance at a KPA is on par with the most influential Cancer Research Institutes. The KPA merits unconditional continued support.

**Very good** → The institutes performance at a KPA is en route to be on par with the most influential Cancer Research Institutes and is nationally speaking at the forefront in the field. The KPA merits continued support, but some efforts are required to improve performance in the KPA.

**Not Competitive** → The institutes performance at a KPA is adequate and considered to be (inter)nationally visible. The work is solid but not sufficiently promising to be supported as it is. Substantial efforts are required to improve performance in the KPA.

**Unsatisfactory** → The Institute performance at a KPA is neither solid nor exciting, flawed in the approach, execution and management. The current KPA is not worthy of pursuing and should be terminated.
3. Assessment conclusions & recommendations

3.1. Overall assessment conclusions

The generous funding of the Oncode Institute, has enabled the use of investigator-specific funds that are not ear-marked for specific projects. This is not only highly appreciated by the scientists but is also proving to be very successful. It allows OI Investigators to explore “high risk/high reward” projects in the field of translational cancer research. In this context, Oncode is tackling some of the most relevant issues in cancer. It allows researchers to change direction rapidly, when change is called for. Naturally, high-risk/high-gain research brings with it an intrinsic acceptance that some studies will fail. This should not dampen but rather sharpen the enthusiasm for exploring the interface between discovery research and medically relevant implementation. Oncode appears to be a novel mode of organization for the funding of biomedical research in the Netherlands, and so far it gets very good marks, from scientists and clinicians alike. The support of young investigators is exemplary. The Management team has built up a highly laudable infrastructure, partially in silico and partially by stimulating collaborations within the network. They have done a first rate job launching this initiative, and appear to have full support of the Investigators. The Valorization Team is exceptional, but it is too early to have the high rate of return they propose. As far as internal organization goes, committee SOPs need to be written and approved. The clinical studies and cancer-specific workshops are excellent initiatives and with some improvements should bear fruit in the second funding period. In summary, Oncode provides and promotes opportunities for cross talk, collaboration, and innovative, high risk high gain research.

Rating: Very good to Exceptional with room for improvement

3.2. Recommendations for continued funding

Please provide key recommendations to increase the operational and strategical performance of the institute.

Terms of reference for committees and management. There has been some progress on diversity within the management and committee structures. However, there was no COI protocols established for the Clinical trial advisory board. More precise documentation of terms of reference would be useful, and clear nomination procedures and maximum term length for advisory board membership should be set, and be shorter than the granting period.

As mentioned above, the centralized mode of funding that enables the establishment of a community committed to common goals is very important, and should not be replaced by more distributive project-specific funding. We believe that Oncode fills a gap that existed in the Dutch granting system for biomedical research.

3.4. KPA 1 Scientific excellence

The scientific excellence of Oncode is to be seen as a measure of the effectiveness to create an environment in which Oncode researchers can reach their maximal innovation potential, through effective implementation of the scientific strategy. The IRC has assessed the scientific excellence of Oncode and has come to the following conclusion:

The panel notes that KPA1, Scientific Excellence, and KPA2, Collaborative Excellence, are closely linked and so have provided a report that combines these two KPA.

The IRC commends Oncode Institute for an excellent performance in both the scientific and the collaborative KPAs. Collectively, the scientific excellence is clearly on par with some of the top cancer institutes worldwide. Also, opportunities for young future leaders of oncology research including clinicians have been increased tremendously. Oncode has demonstrated that by
promoting already existing young talents to connect better, they can increase their added value in oncology research. This will also help and promote recruitment of new leaders from abroad to Oncode.

The IRC notes that Oncode has a broad platform of very strong discovery science projects, that have led to the development of a significant number or excellent collaborations across the board. Examples were given of new collaborations developing between OI Investigators facilitated by the Oncode Institute. In many cases, this allowed OI Investigators to take their research in new directions that lead to rapid advancement of the projects. Also of note, there were many new collaborations between basic and clinical scientists, and clinicians that again have taken the discoveries in new directions, producing exciting pre-clinical data and developing new clinical trials. It is likely that this trajectory will continue to grow in the second phase. This has led to a sense of strong integration between the science and the clinical efforts across Oncode, and has been driven by an open collaborative spirit and the culture that the Oncode leadership has created.

This culture has already led to some impressive successes. The EU IMI funding and collaboration deserve special mention, as does the pro-active approach to valorisation, leading to the successful launch of spin out companies and an excellent pipeline of patents and intellectual property protection. Oncode’s philosophy of sharing its high-end technologies, including single cell analysis, proteomics and organoids is benefitting not only the OI Investigators, but also the broader communities in the host institutions in which these technologies are placed, and the wider scientific community in the Netherlands who are not OI Investigators. Pleasing examples of new immuno-oncology approaches were presented by two investigators, and the opportunity for small molecules to provide useful tools was noted.

The panel acknowledges and applaud the inclusive nature of Oncode toward its junior investigators, post-doctoral fellows and PhD students. The network that Oncode is developing is providing access to new ideas and new technologies that would not otherwise be available to these early career scientists, providing new ways to view their science, and new opportunities. One example is the launch of Single Cell Discoveries by two of Oncode’s most junior scientists. Key to the development of these new collaborations are Oncode’s meetings workshops, which are both topical and general, and which are the drivers of integration across the Institute.

The availability of the Oncode base funds, essentially funds that are not ear-marked for specific projects, is proving to be very successful, and is clearly allowing OI Investigators to explore “high risk/high reward” projects. Their ventures into new areas of exploratory research allow Oncode to tackle some of the most relevant issues in cancer, including very rare tumours. Naturally, a philosophy of high-risk research brings with it an intrinsic acceptance that some of these studies will fail, but this reveals the high ambition of the Leadership and its acceptance that advances generally only come from those brave enough to fail.

**Rating: Exceptional**

**3.5. KPA 2 Collaborative excellence**

The collaborative excellence of Oncode is to be seen as a measure of the quality of the execution of the strategy to drive innovation through collaboration, based on the potential of the Oncode community and the strategy to build a scientific community in which interdisciplinary collaborations are natural, boundaries to collaborate are overcome and a culture of openness and sharing is fostered. The IRC has assessed the collaborative excellence of Oncode and concludes that
they have done an outstanding job in encouraging new cross-disciplinary and cross-institutional collaborations, as described above.

**Rating: Exceptional**

### 3.6. KPA 3 Patient benefit

Patient benefit is to be seen as a measure of the quality of the execution of the strategy to fulfil Oncode's ultimate aspiration to translate Oncode research findings into benefits for patients. The IRC has assessed the patient benefit of Oncode and has come to the following conclusions.

Overall, there is a positive impression of the work ongoing in KP3 to achieve Patient benefit. It is, however, too early for the committee to make a firm judgment. We noticed an interesting and constructive interaction with patients and a clear participation of patients. The OI Investigators mentioned that the tumor-specific meetings organized by Oncode between clinicians and preclinical scientists are stimulating, and have led to new collaborations, projects and grants.

Oncode considers it important to have clinical proof of concept (CPoC) studies. It is not clear which part of the budget is devoted to CPoC studies. Clinicians can be the PI of these studies, yet it was not immediately transparent how they get involved, as there is currently no application or selection process in place for them. Oncode needs to ensure that the benefits of the institute mentioned above are also felt by the clinical collaborators.

OI Investigators repeatedly expressed that they liked the easy access to funds for CPoC studies, and the efficient and rapid access to CPoC funding does benefit translational research. It is worthwhile to critically analyze if realistic, doable clinical studies can be carried out within the Netherlands alone. Particularly for pediatric studies of rare tumors, international collaboration may be critical.

The IRC notes that valorization is considered from early stages in the projects, and this is highly relevant for patient impact, although it is impossible at present to know whether it will result in affordable health care, but for economic benefits from new treatments, these must be affordable. Thus, a consideration of the incidence of the disease is strategically important, even if it may be less important for the individual researcher.

**Challenges for this KPA:** The size of the budget set apart for these studies is not clear and should be defined. The clinical advisory board (CAB) appoints itself, and it is not yet determined how long these appointments last, nor how the all-important turnover (needed to bring new ideas) will be achieved. CPoC projects are selected by the CAB and OEDES team. Some members of the CAB themselves were awarded CPoC funding, which may appear as a conflict of interest. It is important to consider how the selection of CAB members and of clinical investigators is best performed.

The position of certain clinical researchers participating in Oncode funded studies is unclear. The Oncode Leadership should consider whether clinicians involved in Oncode funded trials should be made honorary OI Investigators. Also, efforts to free early career MD-PhDs to devote time to translational research is needed. We note that it is important to overcome hierarchy in the medical establishments for innovative medicine to succeed.

**Rating:** It is somewhat early in the life of Oncode to fully rate this KPA, and the IRC consider the progress to date to be Good. However, with resolution of the challenges outlined above, this KPA has the potential to be Exceptional. The IRC strongly recommends that the Leadership addresses the identified issues with some urgency.
3.7. **KPA 4 Economic benefit**

The economic benefit of Oncode is to be seen as a measure of the ability to create a favorable financial ecosystem for oncology R&D in the Netherlands, through the implementation of a strategy that directs the translation of Oncode research findings into economic benefits. Oncode has set itself an ambitious 15-year goal in which every publicly invested euro will be matched with 1 euro of private investments.

There is good awareness of, and engagement in, the valorization agenda by both senior and junior researchers. The running of events and the provision of training was highly and broadly valued. The focus on Oncology and the range of financial supports that are available are seen as very beneficial by the research community, and are seen as positively supplementing the resources of host institutional Technology Transfer offices. The integration of the Business Development staff in research teams seems to work well with many Oncode staff referencing the Valorization Team’s early engagement with their work.

The IRC has specifically assessed the ability of the Institute to set up and efficiently use a high-quality valorization infrastructure to increase the economic impact of Oncode research findings, and to leverage the investments made by KWF and Dutch government with 0.5 euro in private investment in the first 5 years. Whilst it is still early days in the Oncode journey, it is difficult to see how the KPA4 objective of securing the matching funding of €0.5/€ in private investment in the first 5 years will be achieved, especially when the routes to income are limited. This should not be a hard and fast milestone.

The Bridge Fund investments to date have been reasonably modest and the strategy of investing through loan financing (rather than equity) is perhaps worth another look.

Whilst it is still early, more licensing activity should be considered in the next period.

**Rating:** Overall, the efforts made in this area are **Exceptional.**

3.8. **KPA 5 Affordable Health Care**

The effects of Oncode’s Affordable Health Care strategy are to be seen as a measure of success to create an ecosystem in which research ideas can be translated with maximal societal benefits at affordable cost. As part of its strategy, Oncode aspires to ensure that in 15 years, 20% of its research findings which are put into clinical practice have emanated from the Oncode affordable health care programme. The IRC has assessed the affordable health care activities of Oncode and has come to the following conclusion:

Promoting AHC as an ultimate holy grail action is a highly laudable goal for Oncode. We note that this is a mid- or long-term deliverable package, as it requires the transformation of biomedical advances into real actions that promote sustainability within Health Care systems, which requires societal and political support.

What we have seen to-date are many projects that pursue precision medicine by different means:

- Introduction of predictive (both positive and negative) biomarkers that help to identify populations of patients that may benefit from target-directed therapeutics. In some cases, these biomarkers reduce the target population that meaningfully benefits from the treatment, but in others, the relevant population may expand beyond the initially targeted...
population for the labeled indication for a drug (i.e., in the use of PARP inhibitors beyond patients with tumors harboring BRCA mutations).

- We have also seen examples of synthetic-lethality with demonstrated clinical value (such as BRAF inhibitors combined with anti-EGFR therapies in the BRAFV600E mCRC population). Others are on the way and there appear to be opportunities to repurpose into new therapeutic indications drugs that are off-patent or on expiring patents.

- We note that progress in the CPoC and biomarker discovery is significant, and that identification of the potential clinical value of these actions is advancing properly. Advances in the repurposing program are still limited, largely because of the timelines. An implementation of these advances will require the involvement and cooperation of multiple stakeholders (including but not limited to collaborative clinical research groups, patients’ advocates, payors, members of the civil society) in the long run.

Rating: Again, it is rather too early to be rating this activity, but the indications are positive and the IRC rates this activity Very Good, with the potential to be Exceptional.

3.9. **KPA 6 Organizational and managerial excellence**

Organizational & Managerial efficiency is to be seen as a measure of a) the ability of the organizational set up and governance of Oncode to execute the strategy as outlined in the strategic plan; b) the efficacy of the management strategy to monitor and manage Oncode’s activities and goals and adjust its strategy when required. The IRC has assessed the organizational and managerial excellence of Oncode and has come to the following conclusions:

The Oncode Leadership is congratulated for its achievement, in very short time, of starting with no structures and establishing a working Management Team that is not only functional, but effective and not afraid to take decisions. Mistakes of the past are seen as lessons to be learned, and practical solutions have been implemented. It is noted that the Leadership has created an integrated, interactive and spirited institute that has connected many groups across the Netherlands, leading to new collaborations, projects, funding streams and commercial outputs, in a very short time.

Specifically, the Valorization Team has done an outstanding job and received many positive comments from OI Investigators, post-doctoral fellows and PhD students. To ensure the vitality of this activity, the IRC recommends that a Valorization Board is constituted as soon as possible to provide independent advice and that this Board contains international members.

The establishment of high-end technology support has been excellent and is important for Dutch science even beyond Oncode (see KPA1).

The diversity and inclusion of junior PIs beyond the “inner core” is highly laudable, but we encourage the drive to diversity, and sustained recruitment of women and additional junior PIs.

The Patient outreach program appears to be well managed, interesting and inspiring.

The post-doctoral fellows and PhD students were very happy and well connected to the Institute. The Leadership team could consider whether they would benefit from retreats of their own.

Overall the goal of the Management and Leadership Boards are to maintain the balance of “exploratory high-risk research” and the “relevance for patients”. This they seek to do by marrying the two efforts, and while it is a smart idea, the balance is delicate. So far, they have done an excellent job, but there can be pressures arising if research funding gets tighter.
The IRC acknowledges that some problems arose at the launch of Oncode, but was pleased to see that these have largely been resolved by the Leadership Team and that any remaining issues are being dealt with effectively. The IRC is very optimistic that the Institute is developing in a positive, exciting and productive direction. Their progress thus far merits an exceptional rating.

Specific Challenges facing the management team:

**Assessment and turnover of members:** Smooth assessment of OI Investigators leading to renewal or termination of membership to Oncode will be very important. It is important that mechanisms to achieve this are developed, but it needs to be handled carefully and fairly. With the limited size of the Netherlands scientific community, it is essential that these reviews include input from international members.

**Definition of deliverables:** It would be useful to examine the deliverables at the end of year four and benchmark these against other similar platforms (such as CRUK, Italy, VIB) and where they were at this stage in their development.

**Rating:** The progress of the Organizational and Management Teams is Exceptional.