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ESMO OPEN SCIENCE FOR OPTIMAL CANCER CARE

REVIEW

Health networking on cancer in the European Union: a 'green paper' by the EU Joint Action on Networks of Expertise (JANE)

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Health networking is in principle a formidable instrument to address many challenges posed by cancer, one of the two most common and most lethal non-communicable chronic diseases. The European Union (EU)'s Beating Cancer Plan foresaw the addition of new health networks to the four already existing European Reference Networks on rare cancers: the Network of Comprehensive Cancer Centres and several networks of expertise (NoEs), which will be shortly deployed on items as complex and poor-prognosis cancers, palliative care, survivorship, personalised primary and secondary prevention, omic technologies, hi-tech medical resources, and cancers in adolescents and young adults. The community of experts of the EU Joint Action, due to build such NoEs, has drafted this 'green paper', incorporating 13 open questions, in an effort to foster discussion on some open questions about health networking on cancer in the EU. These affect highly diverse issues such as the following: how gaps in research into the instrument of health networking may be filled; which items lend themselves more to health networking in the EU; what degree of cooperation and harmonisation should be required of EU member states to best exploit health networking and give rise to European networks of national/regional networks; how the idea of subsidiarity may be best interpreted to support health networking in the context of EU treaties, which basically do not include health; how health networks should be funded and with what degree of cooperation between the EU and national levels; whether EU health networks should be shaped as legal entities or could give rise to secondary legal entities, also with a view to fundraising; how health networks should be best shaped to advance cancer research and how the EU regulatory system should be updated to exploit such impulse to health networks, in view of the EU General Data Protection Regulation and the new EU Health Data Space; how artificial intelligence can be exploited today within health networks and to what extent it will be able to overcome challenges such as the current lack of interoperability of electronic health records and the language barrier across the EU; and how health networks should involve patients and their groups, with regard to their formal role within EU health networks as well as their ability to have a say in items such as production of clinical practice guidelines, the design of investigator-driven clinical trials, EU regulatory decisions on medicines and devices, health service data governance, and identification of unmet needs.

Key words: European Union, joint action, health policy, health networking, cancer, expertise

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INTRODUCTION

Cancer is currently the second leading cause of death, and its absolute numbers are rising, given growing life expectancy, with new cases estimated to increase by almost 80% by 2050.[1] Cancer care is increasingly complex, as long as the disease is made up of many different neoplasms, its treatment is highly multidisciplinary, and diagnostic and therapeutic techniques are continuously evolving alongside the impressive pace of clinical and translational research. Its socioeconomic impact is more and more problematic even in affluent societies.[2] Given all these, health networking is in principle a formidable solution to make state-of-the-art treatments available to the highest number of patients at the lowest health and social costs, while fostering research and medical education.[3]

The European Commission (EC) launched Europe's Beating Cancer Plan (EBCP) on the eve of World Cancer Day 2021, with the aim of improving quality of care for patients with cancer in the European Union (EU).[4] It provides a new approach to tackling the cancer care continuum at the EU level, by increasing cooperation among member states (MSs) and the EU, in an area that falls outside the purview of European competences: health.[5] One of the many initiatives highlighted in the innovative document focuses on a group of 'newly created reference networks' that aim to address 'specific, challenging cancer conditions which will benefit from cross-border cooperation and EU expertise'. This request from the EC paved the way for the Joint Action on Networks of Expertise (JANE), which then resulted in the creation of the pathway towards the deployment of seven networks of expertise (NoEs) in the EU.

JANE, a joint action of the EU, i.e. a kind of effort that prioritises those mutual needs of the EU and its MSs that would greatly benefit from joint cooperation at the supranational level, and its follow-up joint action due to start in autumn 2024, comprises most EU MSs as well as several entities. The JANE community created the vision for the aforementioned NoEs, i.e. a new kind of collaborative formal networks, based on the foundational concept of health networking. If this pioneering model works, they may also serve as a pilot for additional networks in other disease areas. During the Joint Action deliberations, it was agreed to foresee the launch of seven NoEs on the following items related to cancer care, given their priority (also within the EBCP) and their liability to be effectively dealt with through health networking: complex and poor-prognosis cancers, palliative care, survivorship, personalised primary and secondary prevention, omic technologies, hi-tech medical resources, and cancers in adolescents and young adults.

While conceiving these new NoEs, the JANE community deemed it wise to reflect on some issues pertaining to health networking itself within the EU, especially considering that some health networks were already in place in the Union, namely the European Reference Networks (ERNs) on rare cancers and rare conditions predisposing to cancer. Moreover, in addition to JANE, the EBCP also envisions the launch of the EU Network of Comprehensive Cancer Centres (CCCs) through a parallel joint action (CraNE).

Based on reflections made within JANE, this green paper aims to serve as a tool to foster discussion within the European oncology community about challenges and opportunities of health networking functioning in the EU.

HEALTH NETWORKS IN THE EU

Characteristically, health networking entails some form of distance collaboration on a planned and regular basis among health care professionals in the fulfilment of one or more items of their mission. Albeit extremely vague, such a definition encompasses an exceedingly wide range of health care activities conducted through networks.

Today, networks underlie every moment of our lives, so that, contrary to the early times of telemedicine, it would be hard to seek their existence in the form of dedicated telematics connections. They can only be viewed as virtual frameworks within which health care professionals, in some way, agree to share part of their professional activities, exploiting everything telematics allows them to use, from a cell phone to a quantum computer.

This said, networks can be classified in several ways.[6] For example, they may be 'formal' or 'informal'. They may be 'professional', where they hinge on professionals' informal willingness to collaborate, or 'institutional', where instead the health care institutions commit to join forces. The former tend to be less governed, more 'fluid' in essence, and the output of bottom-up initiatives by health care professionals, while the latter tend to be more governed, structured, and to be top-down initiatives involving health care administrations, health care systems, or even political bodies at the regional, national, or supranational level. However, this is not always the case: for example, clinical research collaborative groups are long-lasting, successful bottom-up professional networks created to carry out cooperative clinical trials, which are generally governed by rather strict rules. Likewise, some health networks are dedicated to specific items, others to specific territories. The result is a formidable number of highly discrepant efforts, which is more than reasonable given their discrepant targets. In any case, they substantially reshape the everyday life of health care professionals. Clearly, this affects the way health care is delivered and consequently the everyday life of patients.

If one looks at all these, the relative scarcity of dedicated medical literature on the shape and efficacy of health networks sounds striking.[3] Thus, anyone deciding to create a health network, for example in Europe, may not easily find research data about health network models, structures and cost/effectiveness, as well as convincing evidence of the pros and cons of various types of networks in relation to the various goals they may have.

1. A question for the health care community worldwide is how we all could contribute to the advancement of health research on networking, by feeding the medical

literature on this topic, as well as by organising efforts to share and discuss best practices, involving health care professionals, health care administrators, health economists, and so forth.

Over the years, since the dawn of telemedicine, health networks have been established in various areas: from a systems lens (i.e. in transversal areas as emergencies, geographically problematic territories, expensive/scarce medical resource allocation, among others) to a disease-specific lens (e.g. rare cancers, rare diseases, etc.) approach. In the area of oncology, as said, collaborative research groups are a long-standing example of health networking.[7,8] Although these groups were conceived to undertake clinical trials, which otherwise would not have been feasible or much slower, one of their by-products has been some improvement of the quality of care in the community. In other terms, as a matter of fact they served as health networks, in addition to being research networks.

At a European level, attempts at health networking in oncology have been most prevalent for rare cancers.[9] At a national, regional, or local level, networking endeavours have included allocation of scarce medical resources within/across sectors of oncology care, such as palliative care, which must reach out to individual patients well beyond the borders of any cancer hospital. Likewise, health networking has also been deployed to rationalise community oncology delivery, for example, in the field of common cancers within given territories, from large cities to difficult-to-serve areas. The NoEs, conceived by JANE, aim to approach health networking through a systems lens and are institutional as opposed to professional. Before this Joint Action, the EU, through the Cross-border Healthcare Directive (CBHC), gave rise to 24 ERNs on rare diseases, with four linked to rare cancers and rare conditions related to cancer.[10,11] Thus, four cancer ERNs have now had the opportunity to be tested on the ground, although still experimentally.[12,13]

2. An essential question for the whole oncology community, including medical and professional societies and all other fora, is what is the added value of health networking as far as subjects chosen by the EU for its networks are concerned and which are the best network models (formal/informal networks, etc.) to deploy given such subjects. The next obvious question is to what extent such items (rare cancers, poor-prognosis cancers, palliative care, survivorship, personalised prevention, omic technologies, hi-tech medical resources, cancers in adolescents and young adults, as well as cancer care provided by CCCs) actually correspond to the needs of the community and/or whether networking is the best tool to address them and/or whether other networks should follow.

INTEGRATION BETWEEN EU HEALTH NETWORKING AND MEMBER STATES

According to the EU treaties, health is primarily a national competence.[5] However, in certain situations, including serious cross-border threats (e.g. pandemics), the EU has put in place mechanisms allowing countries to coordinate and collaborate responses at the supranational level. This European 'health union' was tested during the COVID-19 pandemic, giving the world a glimpse at its potential. This said, MSs retain full responsibility for organising and funding their own health care systems and delivering health care nationally. Several MSs have federal health care systems, by which health care decisions are made regionally rather than nationally (e.g. Germany, Italy, Spain, etc.). Some MSs are large European states, with several dozen million inhabitants, while others are the size of a large region of bigger states, and necessarily depend on agreements with bordering MSs for at least some of their health care needs. Additionally, a few small countries have limited resources, reflecting some substantial inequalities in cancer care which exist throughout the EU. All these have obvious implications as far as health networks are concerned.[14]

Based on this premise, in a sense EU health networking may be viewed as an exception to EU principles relating to health care. So far, the only example of EU health networks are the ERNs. Generally, they may be deemed to have been proactive in areas like clinical practice guideline production, clinical case discussions, medical education, sharing of clinical research efforts, and the like. However, this is something European health care professionals have always done, through scientific societies and collaborative groups via a distinctive style of bottom-up professional networking. Clearly, ERNs may have strengthened these efforts, but it would be a stretch to say they have changed cancer as perceived by EU citizens. It is well known that the legal tool on which ERNs are based, i.e. the CBHC, does not in practice allow EU patients to travel across borders (and ERNs are there also to limit such travelling, which, in the field of rare diseases, may be an especially pertinent issue). Thus, the work of ERNs is to be praised, but their inherent limitations seem to reflect the limitations of any form of health networking in the EU, unless the rules change. For this to happen, the EU should not necessarily change its treaties, since MSs can always agree to pragmatically devolve part of their sovereignty (as happened with the joint procurement of COVID-19 vaccines).

3. The question then becomes whether and to what extent MSs might contemplate collaborating with each other in the health domain through health networking, whether by simply favouring a model of essentially professional networking or even being ready for more formal networking through supranational agreements, and so forth.

The principle of 'subsidiarity' is a gold standard of EU functioning, as defined in Article 5^3 of the Treaty on European Union.[5] For areas which do not fall within the EU's exclusive jurisdiction, it aims to ensure that decisions are taken at the closest possible level to the citizen, nationally, regionally, or locally. In health, as said, MSs retain their decision-making powers and the EU complements their national policies in areas which necessitate supranational

intervention. In a way, health networks are inherently fit to serve a subsidiarity logic: they can be activated as necessary, i.e. as long as the local resources are not sufficient, in whatever sense. This is especially true as long as an integrated system of networks does exist at both the EU and the national level. For example, EU health networks may be more or less crucial for rare and ultra-rare diseases depending on the local resources, which in turn may well depend on a country's size or its gross domestic product (GDP), etc.

4. The operational question arises as to how the subsidiarity principle can be best interpreted by health networking in the EU. On the other hand, which network activities at the EU level comply most with this founding EU principle, with a view to delivering the best quality of care possible throughout the EU given the variety of local environments? Pilot use cases envisaged by the many networks now due to start in the EU will be crucial, possibly not only for the field of oncology.

In the field of rare cancers, it is generally acknowledged that health networking is useful at national and/or regional levels, and that, to fully express their potential, ERNs on rare cancers should become European networks of national/regional networks.[13] This would avoid sovereignty issues, leaving MSs free to shape them as they see fit, with national/regional networks and institutions simply receiving possible services at the EU level, as needed. In addition, different topics could be served differently, particularly considering the wide array of items covered by NoEs. Besides, the nascent EU Network of CCCs will incorporate cancer centres which may already be organised within national networks, at least in some countries.

5. The open question for the oncology community is how to develop the concept of EU networks as 'networks of networks' (EU networks of national/regional networks), to be effectively deployed in the real world of EU today, in full collaboration with MSs. Another question is to what extent an EU network may be involved in evaluating the needs and/or performance of national networks, including the need to balance the presence of MSs of different size or GDP. This would mean having a say in the governance of national or regional health networks, but should take into account discrepancies among MSs.

SUSTAINABILITY

The 'costs' of health networking have often been overlooked.[7] Health networking is not just a different way for existing facilities to function, nor is it self-sustainable. On the contrary, in order to function, health networks need dedicated infrastructures, i.e. designated human and logistics resources. Most importantly, clinical services provided by health networks necessarily imply some degree of extra medical workload. If an infrastructure is in place, then a health network can regularly fulfil specific functions (e.g. teleconsultations) and/or undertake specific projects (e.g. clinical practice guidelines, etc.). Thus, health network funding should address (i) the infrastructure; (ii) regular network services; and (iii) dedicated network projects. In practice, regular funding could be provided to cover the first two points, while specific funding, for example via grants (including research grants), may cover the last.

That said, from a health care system perspective, health networking is expected to bring about an improvement in the quality of care by making the same quality of care available to a higher number of patients, as if they physically reached out to the best institutions within the network. In addition, both economies of scale and avoided costs are likely (e.g. appropriate frontline surgery may improve results as well as avoid reoperation costs, etc.). From a societal perspective, a decrease in social costs may be expected (as those resulting from health migration). Therefore, health networks may well enable a substantial improvement in cost-effectiveness under several perspectives, although some social costs may ultimately be converted into direct health costs (e.g. decreased health migration is achieved thanks to health networks funded by a health system). However, it is often hard to formally demonstrate such improvements in cost-effectiveness through pragmatic studies, economic models, and the like.

6. An open question about EU health networks is who should pay for their infrastructure: the EU, or MSs, or both? Accordingly, some of their activities should be funded on a regular basis, while others can be funded through *ad hoc* projects. Another open issue is whether the EU should be responsible for funding these projects and to what degree should projects be competitive, given the EU rules, once dedicated EU health networks have been deployed on specific items. Other open questions are how to develop appropriate performance metrics to measure the effectiveness of networks and rationalise their funding and how to study at best their effectiveness and cost-effectiveness.

Many of the health networks existing to date or under construction imply some degree of cooperation between the EU and the national level. For example, ERNs on rare cancers are theoretically EU networks of national networks, which implies the establishment of good cooperation between the EU and the national level. However, if an EU network on rare cancers is funded at the EU level, but no counterpart is funded at the national level, no 'network of networks' will in practice be in place.

On a separate note, EU health networks may address the special needs of small MSs, which inevitably must rely on larger bordering MSs for certain health services. EU health networks are the best tool to accommodate this. On the other hand, resource-constrained MSs have completely different needs, which again health networks could serve best.

7. An issue is how the supranational EU level can/should influence the national level and how the costs of network funding can/should be split. Another open question is how a system of EU networks integrated with national networks can be best organised and

funded, most likely based on some kind of partnership between the EU level and MSs. The question is how all these different needs of MSs can be accommodated within the functioning and the sustainability framework of EU health networks.

Currently, the ERNs are the only example of health networks at the EU level. Despite being created through a legal tool—the CBHC—they are not legal entities, and the mechanism of their funding has been erratic, often through temporary project grants. The EU opted to create both the NoEs and the Network of CCCs through the dedicated 'EU joint action' tool. Their future mechanism of funding remains unclear. On top of that, EU health networks are not, and apparently will not be, legal entities. Thus, for example, EU health networks are unable to carry out any autonomous fundraising. With respect to NoE governance, there may be the opportunity to involve private entities, such as industries or insurance companies. Of course, reliance on corporate financing can create dependencies that may influence research agendas and clinical practices, i.e. can give rise to conflicts of interests.

8. A crucial open question is whether EU health networks can and should be shaped as legal entities or whether they could give rise to the creation of formally independent legal entities to which some of the services they cannot provide could be delegated. Then, in order to best exploit private entities, an open question focuses on how proper oversight can be secured to ensure transparency and accountability, and how possible conflicts of interests can be managed.

INTEGRATION BETWEEN HEALTH CARE AND RESEARCH

Electronic health data are generated by all cancer hospitals, providing what is now called 'real-world evidence', which artificial intelligence (AI) is increasingly able to process in innovative ways.[15,16] Health networks undoubtedly present a formidable opportunity for outcome and epidemiological research as well as for biobanks. Indeed, the integration of health care and research must go beyond traditional boundaries to cultivate an entrepreneurial health care ecosystem actively promoting innovation and knowledge transference. However, this scenario is remarkably new and largely uncharted.

9. Thus, an open question is how health networks can be future-proofed and involved in clinical, translational, and health service research, including how research can be funded in an evolving scenario. A question is how health networks can be exploited to delineate a new health care ecosystem allowing research and innovation through dual health and data networks integrated with hubs, incubators and accelerators, public—private partnerships aimed at promoting networking among academic institutions, and health care providers and industry to foster innovation and translate research into new diagnostic/therapeutic options for patients. In general, the question is how to view networks as resources for innovation and attracting investors, in both the public and private sectors. Of course, a major issue has to do with the variegated administrative and legal landscapes at the national level within the EU.

Part of the research costs are driven by today's administrative constraints of clinical research, especially affecting clinical trials. In this perspective, health networks can help harmonise standard operating procedures, thus enabling clinical trials at reduced costs. On the other side, a key challenge concerns privacy issues related to the secondary use of health data for research. Data protection regulations seem to currently constitute the main barrier to health data exchange in the EU, due to the fragmented implementation of the General Data Protection Regulation (GDPR) across EU MSs.[17] While recital 33 of the GDPR acknowledges the idea of one-time informed consent, by which competent patients could decide to donate their health data and tissues to research, thus effectively enabling the secondary use of health data for research purposes, the interpretations across the EU, unfortunately, are deeply divergent.[18] Hence, in practice both the secondary use of data and the exploitation of biobanks are undermined at the EU level. This said, since the adoption of the GDPR in 2016, numerous other legislative files, such as the Data Governance Act, the Data Act, and the recently adopted regulation for the European Health Data Space (EHDS), will contribute to the already complex environment regarding data use and sharing for health purposes.[19] Specifically, with respect to the EHDS, the EU is in the process of developing a trustworthy legal framework to facilitate access to electronic data across all MSs. It aims to potentially revolutionise the use of data in a secure fashion, in keeping with GDPR. The NoEs may be a 'real-world' opportunity to test the potential of EHDS.

10. The open question is how the research regulatory environment can be updated to best exploit widespread research based on health networking, while keeping research standards as high as possible. At a time when the EU is embarking on praiseworthy efforts as the EHDS, EU bodies should address how to overcome disparities in the interpretation of an EU regulation like the GDPR.

Today, electronic health records (EHRs) are widespread throughout health care institutions, including of course cancer institutes. Thus, a formidable amount of clinical data is variably stored at institutions, which could obviously be shared over a health network. Currently, they are largely underutilised, partly because the large-scale evolving process is still in its infancy, partly because of several other obstacles. The first is the lack of interoperability among EHRs, coupled with the huge diversity in European languages. Clearly, AI will be able to address both the linguistic diversity and lack of interoperability. However, domain-agnostic interoperability is an issue for primary and secondary use of health data. In addition, innovative models based on AI, including federated learning, could help as far as data protection is concerned. Clearly, the investments

required thereto may involve European, national, and institutional levels. Moreover, by leveraging an innovation ecosystem grounded in collaborative networks and consortia of researchers, entrepreneurs, investors, and health care providers, a dynamic environment could be created that accelerates the adoption of innovative solutions, driving the translation of cutting-edge research into marketable products and services and enhancing personalised medicine, ultimately improving patient outcomes.

11. A question is how to make sure that innovation allowed by AI can be deployed in the real world of EHRs within health networks, going beyond the stage of demonstration projects, to address both linguistic diversity and the lack of interoperability of IT tools. Another question may be how networks could act as pilots to bring AI into the real world, to address interoperability and data integration issues, and how to meet the legal and ethical requirements pertaining to the use of AI over these networks. A prevailing issue is also how to set up a supportive regulatory environment by balancing the need to ensure patient safety with the urgency of translating research into clinical practice and commercial products. This would require harmonising regulations across diverse legal and administrative landscapes, streamlining processes to reduce delays, and fostering collaboration between regulatory bodies, health care providers, and industry. The networks may facilitate the creation of a framework that accelerates innovation while securing high ethical standards, ensuring that new therapies and technologies reach patients both swiftly and safely.

PATIENT INVOLVEMENT

At a time of empowerment and engagement of patients throughout their clinical journey, it is vital for them to be actively involved in the shaping and functioning of crucial tools as health networks.[20] In the end, they are the 'customers' of health networks, so that the kind of involvement they have in EU health networks may be what makes the difference. Currently, patient advocacy groups are involved in ERNs and participate in their governing bodies. However, their role is poorly defined, considering that only health care providers, i.e. health care institutions, can be full members of ERNs, not, say, patient advocacy groups.

12. Thus, how to implement patient participation in EU health networks, i.e. formally, financially, etc., remains an open item for discussion. Another important issue concerns the process of selecting patient advocacy groups, according to their geographical scope and specific domains.

That said, patient advocacy groups are very powerful in the European oncology community and are currently trying to envisage innovative ways to shape their roles within health networks.

13. In general, there is room for reflection about how to involve patient groups in some services which EU health networks may hopefully provide, especially in regard to the production of clinical practice guidelines, the conception and design of clinical trials, the regulatory process for medicines and medical devices, as well as health service assessment, data governance, unveiling unmet needs, etc.

CONCLUSION

NoEs, as conceived by the JANE community in close partnership with most European stakeholders, hold the promise of creating a new way of providing high-quality care to all patients with cancer in the EU, at least in some cancer care areas. Potentially, they will also serve as a pilot for care delivery within and across disease areas (at the EU level but also with a view to other areas of the globe). However, in spite of the ambition to create these novel NoEs, the community is walking on an unpaved path, with numerous open questions surrounding health networks being raised. With this green paper and its open questions, JANE would like to encourage discussions within the oncology community, to create the best possible NoEs but also to improve the tool of health networking as such in Europe. In principle it is a formidable tool for Europe. We need to pay attention to the tool.

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