European Journal of Cancer 135 (2020) 1–7

Available online at www.sciencedirect.com

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Review

Conceptual framework for precision cancer medicine in Germany: Consensus statement of the *Deutsche Krebshilfe* working group 'Molecular Diagnostics and Therapy'

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https://doi.org/10.1016/j.ejca.2020.04.019

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Received 21 April 2020; accepted 23 April 2020

KEYWORDS
Precision medicine;
Precision oncology;
Molecular tumour board;
Molecular diagnostics;
Genomic profiling

Abstract Precision cancer medicine (PCM) holds great promises to offer more effective therapies to patients based on molecular profiling of their individual tumours. Although the PCM approach seems intuitive, multiple conceptional and structural challenges interfere with the broad implementation of PCM into clinical practice. Accordingly, concerted national and international efforts are needed to guide the further development and broad adoption of PCM in Germany. With support of the 'German Cancer Aid' (*Deutsche Krebshilfe [DKH]*) a task force '*Molecular Diagnostics and Therapy'* was implemented. In two workshops supported by the DKH, delegates from the fourteen comprehensive cancer centresidentified key topics essential to implement quality-guided, harmonized and adaptable PCM. Based on an online questionnaire and using a modified Delphi approach, nine statements were drafted and evaluated within the group. These statements could serve as a basis to define a collaborative strategy for PCM in the future with the aim to sustain and further improve its quality.

1. Introduction

Based on molecular tumour profiling, precision cancer medicine (PCM) aims to identify tumour-specific alterations to offer patients tailored, more effective and safer treatments. This concept has seen remarkable successes in various malignancies, such as the implementation of tyrosine kinase inhibitors in the therapy of chronic myeloid leukaemia or of HER2 antibodies in the treatment of breast cancer. Consequently, these results have fuelled optimism that this therapeutic concept can be delivered to the majority of cancer patients. Furthermore, with the increasing use of high-throughput next-generation sequencing in oncology, molecular profiles of tumour tissue become increasingly available raising the hope to obtain meaningful and applicable information for our patients. However, a number of significant challenges are to be considered with regards to PCM. These challenges are complex and wide ranging and include lack of evidence and knowledge, reimbursement issues and missing access to targeted agents. Overcoming these challenges on a local, national and international level will decide on the success or failure of PCM.

In Germany, PCM is mainly practiced at academic institutions. However, national harmonization efforts are starting but are still fragmented. To facilitate exchange between academic centres and to devise a strategy for the future directions of PCM in Germany, a task force 'Molecular Diagnostics and Therapy' within the framework of the *Deutsche Krebshilfe* (DKH) supported comprehensive cancer centres (CCCs)-Network was

established. Based on an online questionnaire, this task force defined challenges required to be addressed for successful implementation of PCM. During two workshops, these challenges were discussed within the group and the general framework for a consensus paper was defined. In total, nine statements covering various aspects of PCM were drafted and distributed within the group. Using a modified Delphi approach, these statements were refined within a stepwise procedure and consented by the members of the group. These nine statements are presented and discussed here to constitute a framework for future activities and to guide broad clinical implementation of PCM in Germany.

2. Methods

Following the first workshop, an online questionnaire consisting of thirty items was devised to define the current status and the challenges encountered in the PCM programs of the fourteen German DKH CCCs. Based on the answers of the participants, six overarching topics were defined highlighting major challenges in PCM:

1. Integration of molecular profiling into clinical practice
2. Definition of actionable targets and harmonization of reporting
3. Composition and tasks of a 'Molecular tumour board' (MTB)
4. Access to therapies and implementation of treatment recommendations
5. Structured collection of clinical data and clinical follow-up
6. Financial compensation of molecular diagnostics and therapy

These six topics were consented within the group during the second presence workshop. As a next step, a total of nine statements focussing on different aspects of the core topics were drafted. These statements were again distributed in the group. Members of the group could add comments, accept or dismiss statements. Following a modified Delphi-process, statements were deemed as accepted if $\geq$ 80% of the participants agreed with a statement. During the first round, five of nine statements were accepted with minor changes. Accordingly, four statements were adjusted, sent for a second round of reviews and subsequently consented by the group.

Statement 1 – chances and limitations of comprehensive genomic profiling (education)

'Treating physicians should be aware of the chances and limitations of current diagnostic modalities to offer the right testing to their individual patients and communicate them clearly. Proper measures of education should be offered in this regard.'

PCM is a rapidly evolving field. This is true for both technical, as well as medical advances. The complexity of comprehensive genomic testing and the potential therapeutic consequences pose new challenges to the treating physician: (i) PCM frequently operates outside of the classical concept of histology-driven therapies based on large-scale clinical trials [1,2]; (ii) only a proportion of mutations identified so far have functional data suggesting that serve as therapeutic targets, (iii) interpretation of results often requires detailed knowledge of molecular alterations in the context of a given malignancy; and (iv) molecular oncology is not sufficiently covered by curricula of medical schools. Accordingly, physicians are not prepared to interpret test results and draw adequate therapeutic conclusions [3]. Consequently, misinterpretation of molecular results carries a risk of incorrect treatment decisions [4]. In PCM, the need for interdisciplinary teamwork is more evident than ever to ensure proper integration of medical and scientific knowledge into patients' management. In the future, medical school will need to integrate molecular oncology into their curricula to prepare young doctors for the challenges ahead [5].

Statement 2 – cooperation of treating physicians and pathologists

'Treating physicians should cooperate with molecular pathologists to guarantee availability of state-of-the-art molecular tumour profiling.'

PCM strongly relies on the cooperation between different specialities. In recent years, academic pathology, as well as hematology/medical oncology have been instrumental in developing and refining the methodological tools constituting the basis for molecular tumour profiling. Progress in molecular pathology is fast and leads to a rapid improvement of availability, broadness and sensitivity of testing. This leads to a considerable change in the classic role of the pathologist towards molecular pathology [6]. As mentioned above, the landscape of medical oncology is changing. Novel therapeutics linked to specific genomic alterations in ever smaller subgroups are rapidly evolving and may have a dramatic impact on the course of disease across different entities [7,8]. Accordingly, medical oncologists and pathologists need to work together to assure the profit of their patients from the rapid progress in both fields. Only a close cooperation will guarantee availability and clinical translation of comprehensive state of the art diagnostics to identify alterations that could change the therapeutic management of patients or allow for inclusion into a molecularly stratified clinical trial.

Statement 3 – reporting of testing results

'Cancer centers should consent a harmonized reporting of genomic alterations.'

To facilitate harmonization of PCM across centres, a crucial step is the implementation of a common reporting of results from comprehensive genomic profiling. Ideally, reports from (molecular) pathology distinguish between known pathogenic and (likely) benign conditions and variants of unknown significance and provide information of clinical significance of the alterations reported. In this area, knowledge is continuously evolving. Accordingly, the continuous update, curation and validation of variants in the respective databases are of utmost importance. Harmonized reporting algorithms will allow an exchange of reports between centres and will support documentation in shared clinico-genomics databases (see in the following context).

Statement 4 – clinical implications of comprehensive genomic profiling

'Clinical implications of genomic and transcriptional alterations should be consented by (molecular) pathologists and clinicians. Additional support can be provided by bioinformaticians as well as geneticists where needed. This should preferentially be realized in dedicated interdisciplinary MTBs and by development of an evidence framework supported by prospective data collection, clinical-molecular registry approaches and early clinical trials.'

A major challenge in PCM is insufficient evidence that treatment decisions based on comprehensive genomic profiling lead to a meaningful clinical benefit in patients [1,2]. To critical assess the (potential) pathogenic role [9] of a given genomic alteration, its druggability/actionability and the resulting clinical implication, different classification systems have been proposed [10–15]. However, interchangeability across different systems is limited and there is no general consensus on which system to use. In fact, a recent international survey found significant heterogeneity not only with regard to the assessment of genomic alterations as actionable but also with regards to treatment recommendations across different academic MTBs [16]. To allow for a more comparable and systematic conduct of PCM, centres should try to consent harmonized approaches to clinically grade genomic alterations and issue treatment recommendations. In the future, the implementation of functional testing to prioritize molecular targets and treatments could be considered to complement PCM programs [17]. Treatment should preferentially be conducted within molecularly stratified clinical trials to fill existing knowledge gaps and collect data in a structured and sustainable fashion.

Statement 5 – composition of a MTB

'To provide greatest effectiveness, MTBs need to follow clearly stated infrastructural requirements, which allow harmonization across different cancer centers. As a minimal requirement, MTBs shall include a molecular pathologist, the treating oncologist (e.g. from the fields of hematology/medical oncology, dermato-oncology, neuro-oncology, and so on.), oncologists with expertise in the different subspecialties and ideally a geneticist, a bioinformatician, as well as a specialist for molecular biology.'

Generally, MTBs deal with a broad variety of malignant diseases, as most MTBs discuss cases from all subspecialities of oncology. Furthermore, and in contrast to other (organ/disease-specific) tumour boards, the fields of molecular pathology and molecular biology add another layer of complexity to these highly specialized boards. Accordingly, a broad spectrum of experts is needed to address all aspects of PCM to determine the optimal strategy for any given patient. Various different (single-center) experiences have been reported in the literature and all of them come to the conclusion that the hurdles of PCM can only be mastered in a trans-institutional and interdisciplinary approach [18–24].

We strongly believe that currently only dedicated (academic) centres have the infrastructural and personal requirements to meet these high standards and to overcome existing hurdles in a sustainable and scalable way.

Statement 6 – access to adequate therapy

'Access to targeted therapies after identification of druggable targets by molecular profiling is insufficient. Consented efforts are needed to overcome this problem: (I) Concentration of PCM at specialized centers could provide a rationale for payers to cover 'off label' treatment in a structured environment. (II) Clinical trials offering treatment for rare genetic alterations need to be made available to a network of participating centers.'

Even if molecular alterations are identified through comprehensive genomic profiling and assessed as actionable by the MTB, resulting treatment recommendations often are not implemented into patient care. Although reasons are multifaceted, access to targeted agents is the greatest issue. Even if these agents are available, off label use is mostly not covered by payers due to insufficient evidence of activity. Harmonized and well-structured PCM programs in highly specialized centres could create a rationale for payers to allow and cover molecular-driven treatment. Payers, authorities and PCM centres could engage in strategic partnerships to ensure management of cancer patients in a scientific and structured environment. Such constructs could allow for concentration of patients at expert centres and strengthen the faith in PCM. At the same time, centralization of patients at specialized centres would facilitate improved recruitment of patients into molecularly stratified clinical trials as more patients would undergo comprehensive genomic profiling and chances of picking up rare alterations would rise. These centres should implement outreach activities and cooperate with

other hospitals and caregivers to ensure access to care for all patients.

Innovative structures such as the 'Center for personalized Medicine' (Zentrum für personalisierte Medizin - ZPM) in Baden-Württemberg, the Germany-wide NCT/DKTK MASTER initiative [21] and the national Network Genomic Medicine (nationales Netzwerk genomische Medizin - nNGM) aiming to provide NGS testing to the majority of patients with non–small-cell lung cancer are prime examples on how to expand the reach of local/regional PCM initiatives on a national scale.

Statement 7 – clinico-genomic databases and bioinformatics

'Structured and harmonized collection of patient data in clinico-genomic databases supported by adequate bioinformatics is imperative in PCM. This will not only allow to evaluate the benefit from individualized treatment approaches but also to properly tailor the process by creation of learning systems.'

As outlined previously, the underlying evidence for broad implementation of PCM in clinical practice is still scare. This is due to the complexity of the approach and the individualization of treatment. Without collaborative harmonization efforts, generation of evidence in these individualized settings becomes a major obstacle [2]. In fact, generating further evidence is of utmost importance to build confidence in PCM and to justify its use to patients, payers and regulatory authorities. The nature of PCM is use of targeted agents based on a molecular profile rather than on a given entity. Accordingly, generation of reference data for clinical trials or even for an extension of existing drug labels is challenging. One way to address this issue is the set-up of clinical trial grad registries based on consented core data sets [1,2,25–29]. In recent years, structured collection of real-world data (RWD) has emerged as a new option to generate evidence in oncology. RWD data certainly differ from evidence derived from prospective clinical trials, but they may add to existing knowledge in that they reflect a broader subset of patients and practice settings than those typically represented on clinical trials [26,30,31]. In the future, we envision not only a regional, but a national and preferably international clinico-genomics database allowing for prospective collection of treatment outcomes based on PCM approaches. This vision will require concerted efforts to allow with regards to patients' consent, data structure and security. If realized, such registries would not only be an invaluable source of clinical and scientific knowledge but would also allow for novel (bio)informatics approaches to analyse and structure complex data.

Statement 8 – financing

'PCM is expensive. To ensure high-quality diagnostics, comprehensive medical management and cost-effectiveness and to prevent repetitive diagnostic procedures, PCM should preferably be concentrated at specialized centers. These centers should enter a dialogue with payers to establish reimbursement modalities for all aspects (molecular diagnostics, patient management and counseling, as well as personalized treatment) of PCM.'

There are strong arguments that the complexities of PCM require its concentration at dedicated centres that offer the full scientific, diagnostic and therapeutic spectrum. Although quality of treatment is the priority issue in this regard, the potential cost increase for diagnostic testing and medication use should be taken into consideration. To prevent the costly and potentially harmful overuse of molecular testing and targeted agents outside of dedicated programs, all stakeholders involved (academic centres, health insurance payers, regulatory agencies, and so on) should enter a dialogue to create sustainable reimbursement models for PCM. This will allow structured use of these (costly) tools and prevent unnecessary testing and treatment outside of (existing) clinical indications. Measures to ensure scientifically sound and cost-conscious implementation of PCM might include a mandatory requirement for discussion of test results in a MTB that fulfils standardized criteria (statement 5), as a prerequisite for reimbursement. Finally, cost-effectiveness of available and future molecular tests should be constantly evaluated to select the techniques with the highest impact in terms of successfully treated patients. In the same setting, cost-effectiveness of targeted treatments needs to be addressed.

Statement 9 – counselling

'Extended molecular profiling needs to be embedded into adequate counseling not only by the treating oncologist but also by other experts such as human geneticists and psycho-oncologists.'

The broadening use of comprehensive genomic profiling in (advanced) cancers creates great expectations in patients (and doctors) [32]. It is imperative that patients are adequately counselled with regards to potential outcomes of genomic testing [33,34]. Furthermore, patients need to be aware that the evidence for these novel approaches is often less solid than for more 'conventional' therapeutic modalities in oncology (see previously). These issues have to be addressed by counselling offered by experienced oncologists and/or psycho-oncologists.

Finally, genomic profiling of a tumor can yield results that point towards a potential inherited alteration or cancer syndrome [35]. Patients need to be informed upfront about the possibility of incidental findings and counselled appropriately. Specialized clinical geneticists have to be involved in the discussion about appropriate criteria for reporting incidental germline findings arising from genomic profiling of tumor tissue [36].

3. Conclusion and further directions

Here, we report consensus statements covering different aspects of PCM and its implementation into clinical practice. These statements serve as a basis for future collaborative efforts to further develop and expand PCM within the CCC network to provide optimal care for cancer patients across Germany.

Conflict of interest statement

The authors declare no conflict of interest related to this work.

Acknowledgements

The authors thank the German Cancer Aid (Deutsche Krebshilfe) for support of the activities of the Working Group '*Molecular Diagnostics and Therapy*'.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2020.04.019.

Appendix B

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