Opportunities and challenges in oncology and molecular testing: the Belgian strategy

A. Hébrant, Ir, PhD[1], E. Van Valckenborgh, PhD[1], R. Salgado, MD, PhD[2], G. Froyen, PhD[3], F. Hulstaert, MD[4], D. Roberfroid, MD, PhD[4], S. Tejpar, MD, PhD[5], A. Jouret-Mourin, MD, PhD[6], M. Van den Bulcke, PhD[1], A. Waeytens, PhD[7]

SUMMARY

Molecular diagnostics in cancer aiming at improving diagnosis, prognosis and treatment are constantly exposed to new opportunities and challenges. The Belgian Commission of Personalised Medicine (ComPerMed) has been created to advise the Federal Government on all matters related to personalised medicine in oncology, including the reimbursement of molecular tests. Here, we propose the Belgian strategy for molecular testing within a scientific based framework and its implementation in the Belgian healthcare system. For each tested biomarker a clinical test level is attached, which is key to establish the relevance of the test and to define the reimbursement.

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INTRODUCTION

Personalised medicine is defined as 'a medical model using the characteristics of individuals' phenotypes and genotypes (e.g. molecular profiling, medical imaging, and lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time'.[1] Based on rapid advances in biotechnology, including massively parallel sequencing or next generation sequencing (NGS), novel biomarkers and targeted drugs are being developed, mainly in the cancer field.

A systematic evaluation of these new approaches is required in order to optimally develop and maintain personalised medicine, ensuring that treatment is safe and effective for patients in order to give to the physician and the healthcare system the level of confidence needed for optimal treatment decisions.[2]

For this purpose, it is essential to establish for each molecular test 1) the analytical validity (technical performance), 2) the clinical validity (diagnostic accuracy), 3) the clinical utility (probability that the test will lead to health benefits relative to the current standard), and 4) its cost-effectiveness.[3,4]

ANALYTICAL VALIDATION

The objective of analytical validation is to demonstrate that the entire molecular test, including the pre- and post-analyt-

[1]Cancer Centre, Scientific Institute of Public Health (WIV-ISP), Brussels, Belgium, [2]Breast Cancer Translational Research Laboratory, Institut Jules Bordet, Brussels, Belgium and Department of Pathology, GZA Antwerp, Antwerp, Belgium, [3]Department of Clinical Biology, Jessa Hospital, Hasselt, Belgium, [4]Belgian Health Care Knowledge Centre (KCE), Brussels, Belgium, [5]Molecular Digestive Oncology , KU Leuven, Leuven, Belgium, [6]Department of Pathology, Cliniques Universitaires St Luc, Brussels, Belgium, [7]Department of Pharmaceutical Policy, National Institute for Health and Disability Insurance (RIZIV/INAMI), Brussels, Belgium.

Please send all correspondence to: A. Hébrant, Ir, PhD, Juliette Wytsman 14, 1050 Brussels, Belgium, tel: +32 2 642 57 32, email: aline.hebrant@wiv-isp.be.

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ical steps, is able to accurately and reliably measure the biomarker of interest.[5] During the analytical validation process, the test performance (e.g. limit of detection, analytical sensitivity, specificity, precision (reproducibility and repeatability) and accuracy) is determined in the setting in which the test will be performed.[6]

Actually, for some molecular tests, there can be large variability between laboratories such as a variable background noise and different thresholds applied. Moreover, the estimation of the cellularity of a tumour or the interpretation of variants can lead to different test results. In order to harmonise the analytical procedure as well as the test result and interpretation, clear and unambiguous guidelines for clinical practice in molecular diagnostics are needed. These guidelines will also be very helpful for the Belgian Federal accreditation organisation (BELAC).

A standardised label for *in vitro* diagnostic (IVD) tests allows more transparency on the test performance characteristics.[7] In Europe, the molecular tests (including reagents and instruments) are governed by the EC directive for IVD.[8] The product that fulfils the prerequisite set of this directive can be CE-marked. This directive is currently being updated and will integrate the concepts of analytical and clinical validation and will put more emphasis on the quality of the testing methods and the scientific evidence for the use of a particular molecular test.[8] Even though national and/or international guidelines already exist for most molecular tests, they are relatively vague, probably because of the diversity of the different testing platforms and experimental protocols. In order to address this problem, professional organisations and accrediting entities need to develop evidence based guidance documents, through interdisciplinary collaborations.[9]

CLINICAL VALIDATION

The clinical validation aims to determine how well the test predicts the presence or absence of clinically relevant phenotypes in the population under investigation.[10] In practice, clinical validity implies how robustly and reliable the molecular test separates the investigated population into two or more distinct groups, with different biological characteristics or clinical outcomes (clinical sensitivity and specificity and positive and negative predictive value).[11]

Clinical validation studies have to report on the strength of an association between the molecular test and the disease by using useful metrics e.g. the presence or absence of a specific mutation, or a positive or negative result of an immunohistochemistry test.[10]

CLINICAL UTILITY AND TEST LEVELS

A molecular test aims to define particular biological characteristics of a patient and will therefore allow optimal clinical decisions by establishing the diagnosis, providing information on prognosis or predicting sensitivity or resistance to therapy.[4,10] An ideal molecular test will identify 100% of the patients who will respond to the therapy thus having a sensitivity of 100% (100% true positives) and will not be positive for any of the non-responders, corresponding to a specificity of 100% (0% false positives).[6] As most molecular tests are not ideal however, a test is considered useful if the result informs on diagnostic, prognostic or therapeutic value leading to improved patient care. Such an improvement could be the selection of patients eligible for specific therapies or clinical trials, or by changing patient management decision compared to current practice.[6,11] Clinical utility refers to the evaluation of the benefit/risk ratio resulting from molecular testing and the likelihood that the test might lead to an improved outcome for the patient.[4]

To evaluate the clinical utility of a molecular test, a level of evidence as those defined by GRADE should be assigned to each test utility (therapeutic, prognostic or therapeutic utility), which will ensure the relevance of the test for a specific clinical question.[12,13] However, for the rapidly emerging multiplex tests that include many different targets, e.g. NGS panels including whole genes or hotspot regions of genes only, a systematic approach, associating each variant with a test utility (diagnostic, prognostic, or therapeutic) would require many randomised controlled clinical trials.

Moreover, randomised controlled clinical trials for biomarkers with a low penetrance (identifying small populations), which occur more frequently nowadays, are becoming more challenging and costly as it is more difficult to recruit patients. Nevertheless, the sample size may be lower as the effect size of targeted treatments could reasonably be expected to be larger compared with other forms of treatment.

Nowadays, several institutional test levels are available such as those from OncoKB (http://oncokb.org/#/levels) and MD Anderson (https://pct.mdanderson.org/home). These levels are linked to clinical guidelines and standard of care, expert's opinion and approved drugs. These test levels are not formal levels of evidence such as those defined by GRADE as no systematic reviews and randomised controlled clinical trials that demonstrate an improved clinical outcome in patients who have received treatment based upon a test result, compared to those who have not, are taken into consideration.[12]

COST-EFFECTIVENESS AND BUDGET IMPACT OF THE TEST

The primary goal of health care policy is to maximise the health of the population within the limits of the available resources and within an ethical framework built on equity and

solidarity principles, which implies evaluation of the cost-effectiveness of treatments.[14] Cost-effectiveness and cost-utility analyses consider the incremental outcomes in terms of life years gained or quality adjusted life years gained in comparison with the incremental costs of the intervention, relative to the standard of care. In a cost-effectiveness and cost-utility analyses, the sensitivity and specificity of the test and the prevalence of the biomarker have a major impact and need to be taken into account.[6,15,16] Finally, a budget impact analysis is also necessary to inform short-term costs and budget (re-)allocation.[6] Budget impact analyses should include all the relevant parameters, not only costs for running the tests but also costs for validation, EQA, interpretation, overhead and also possible economies of scale. Ideally, funding for a new test type that will replace another one should ideally come from the same budget.[6]

OPPORTUNITIES AND CHALLENGES

Next to the identification and evaluation of these critical variables for molecular diagnostics, the implementation of personalised medicine in Belgium faces some additional challenges. Firstly, the reimbursement of diagnostic tests lags behind the current daily practice and the reimbursement of drugs.

Secondly, the implementation of the NGS technology in clinical daily practice and the massive amount of genomic data such technology generates, challenge current practices in our hospitals. There is a need 1) for more harmonisation of the interpretation of the data between different laboratories in different hospitals, e.g. by data sharing and by using hospital overarching molecular-discussion platforms (also called Molecular Advisory Boards (MABs)), 2) for continuous education to keep clinicians, pathologists and geneticists up-to-date with the NGS technologies and the interpretation of the genomic data, 3) for the development of a database to make a clear link between the test results and the available clinical trials, and finally, 4) for appropriate guidance on patient management after a biomarker test result.

Hospital care networks are currently being established in Belgium and could help to realise the centralisation of NGS testing. The benefits of networks are 1) the integration of expertise in complex diagnosis and treatment; 2) the expansion and linking of existing genomic medicine implementation efforts; 3) the development of new collaborative projects and methods for genomic implementation in diverse settings and populations; 4) the larger evidence base of outcomes following the use of genomic information for clinical care, and 5) the greater ease to define, share and disseminate the best practices of genomic medicine implementation, diffusion and sustainability in diverse settings. Networks of hospitals may thus facilitate the following situations that are unmet: 1) access to innovative drugs with proper documentation of safety activity which is of utmost importance for the health care providers, and 2) promote the development of a nationwide database containing specific genomic information in various histological types of cancer.

COMMISSION OF PERSONALISED MEDICINE: COMPERMED

To provide access to the NGS technology in our routine diagnostics in (haemato)-oncology, the Belgian federal government has financed an implementation project entitled "Road book Personalised medicine: the introduction of next-generation in routine diagnostics in oncology and haemato-oncology (2016-2020)".[17] The Belgian Commission of Personalised Medicine (ComPerMed) was created in 2015 and includes representatives of all professional organisations directly involved in the domain of personalised medicine, including experts from the Belgian Society for Human Genetics, the College of Oncology, the Commission of Pathology and the Commission of Clinical Biology. To address different research issues, working groups are established with Belgian oncologists, haematologists, pathologists, clinical biologists, geneticists and other scientists. The objective of the ComPerMed is to act as a national advisory board on new developments and insights in personalised medicine. With this aim, it supports decision making on reimbursement issues in personalised medicine and advises the Platform Companion Diagnostics, a permanent mixed working group of the Commission for Reimbursement of Medicines (CRM) and the Technical Medical Council (TMC), which are themselves the competent reimbursement commissions for medicines and diagnostic tests respectively, at the Belgian reimbursement agency National Institute for Health and Disability Insurance (NIHDI) or RIZIV/INAMI. This platform, launched in January 2016, aims to reinforce the link between the reimbursement of a molecular test and corresponding therapy and to install coherent reimbursement decisions for the different components of personalised medicine.

In order to advise the Platform CDx on the clinical utility of the NGS, ComPerMed started with a systematic evaluation of all molecular tests currently performed in clinical routine in Belgium for each tumour type, with regard to their test utility (diagnostic, prognostic or therapeutic), and then assigned, for each of them, a test level. With the purpose of harmonising healthcare decisions in molecular testing in Belgium, the experts of the ComPerMed selected the OncoKB test levels and adapted it to the Belgian situation (*Figure 1*). Three test levels were determined, with level 1 representing the most priority for the selection of the test by the policy makers. These

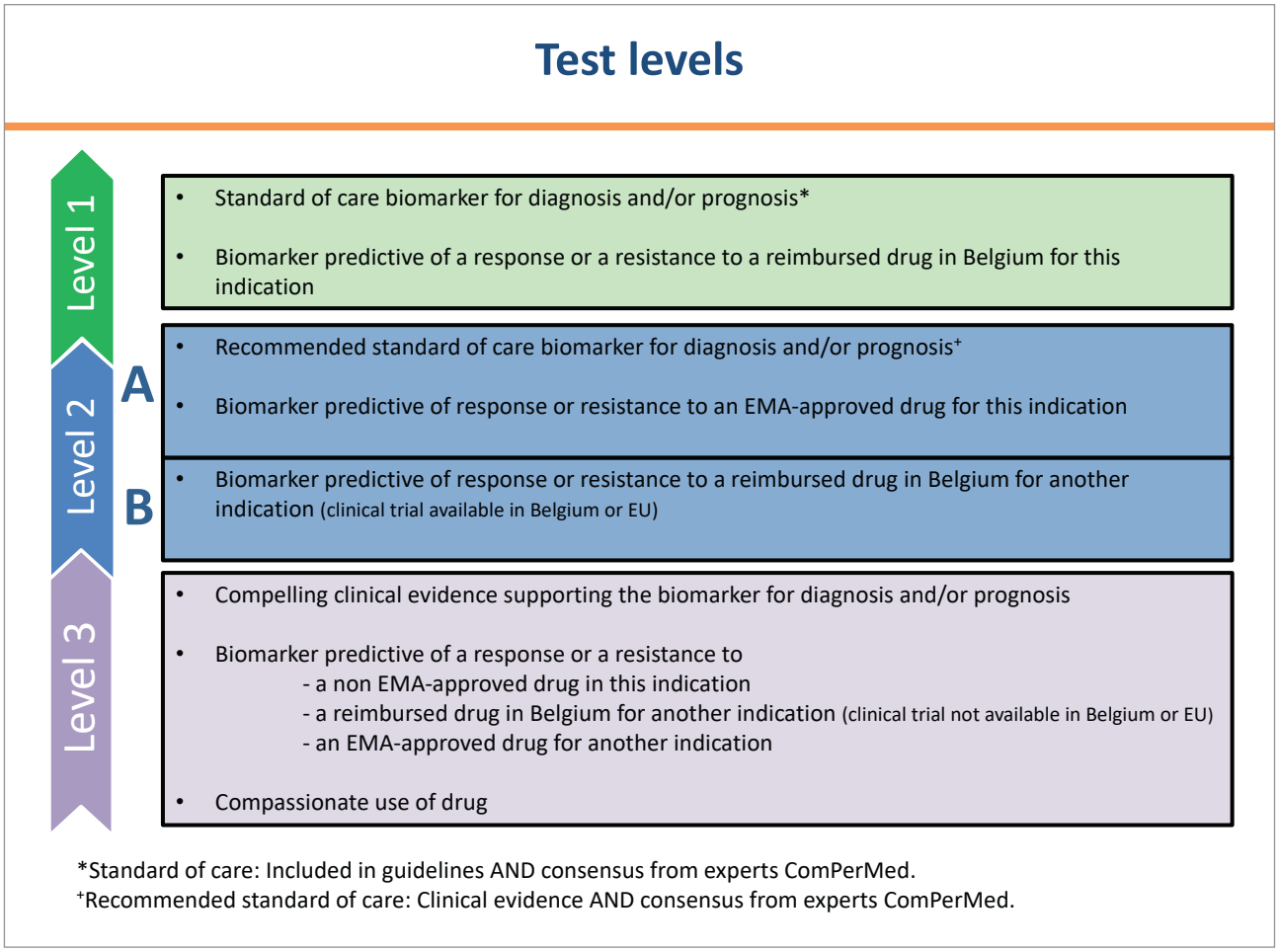

FIGURE 1.

test levels are linked to the standard of care and to reimbursed treatments in Belgium. Common test levels should allow easy implementation of biomarker testing into clinical practice as well as facilitate the development of reimbursement criteria.

In a second step, clinical practice guidelines on molecular testing in different tumour types will be established. Expert groups of the ComPerMed started to propose algorithms representing the sequential molecular tests for each tumour type. Each molecular test is annotated with its test utility (diagnosis, prognosis or therapy), its test level and a brief test description. Incidence of the tumour type is also indicated. The final algorithm of each individual tumour type is the result of a consensus of 30-40 Belgian experts of several hospitals, both academic as well as non-academic. For each tumour type, these algorithms will be completed with information on technical requirements of the molecular tests (sample, validation, pre-analytical, analytical, and post-analytical requirements). Both the evaluation of the test levels and the clinical practice guidelines will be updated regularly. Finally, these algorithms will be made available on a website in 2018, and for each tumour type, will contain information on technical requirements (e.g. guidelines) of the molecular tests and tumour incidence.

In collaboration with HealthData, ComPerMed is developing a procedure for a national NGS data collection for all reimbursed NGS tests in Belgium, starting in 2018. HealthData, developed by ISP-WIV and financed by the NIHDI/INAMI/RIZIV, has the main objective to facilitate the data exchange between healthcare professionals and researchers, and to promote data recording to increase public health knowledge in Belgium. Consistent national data collection on molecular tests, treatments and patient outcomes will provide very useful information to healthcare providers on the appropriateness of molecular tests and their clinical decisions.[3,18]

CONCLUSION

To conclude, a systematic evaluation of the new molecular tests in cancer is required in order to optimally improve diagnosis, prognosis and treatment and to develop and maintain personalised medicine. A national data collection will allow the identification of candidate molecular tests with potential clinical utility by assessing their benefits e.g. by linking the molecular tests, the targeted therapies and the clinical outcome, and will allow harmonising the interpretation of test results such as variant interpretation in NGS. Test levels have

KEY MESSAGES FOR CLINICAL PRACTICE

It is essential to establish for each molecular test:

1. **analytical validity (technical performance);**
2. **clinical validity (diagnostic accuracy);**
3. **clinical utility (probability that the test will lead to health benefits relative to the current standard);**
4. **cost-effectiveness ratio.**

In particular, for the NGS tests, the following points are important:

1. **harmonisation of the interpretation of the data among the laboratories by data sharing and by using the Molecular Advisory Boards (MABs);**
2. **continuous education to keep clinicians, pathologists and geneticists up-to-date with NGS technologies and the interpretation of the genomic data;**
3. **database to make a clear link between the test results, available clinical trials and outcome;**
4. **appropriate guidance on patient management after a biomarker test result.**

to be used as a first step to identify molecular test with potential clinical utility. Assessing the actual clinical utility of such tests should be based on sound scientific evidence, such as randomised clinical trials.

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