The ABCs of molecular diagnostic testing of CNS tumors: acceptance, benefits, costs

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In the last decade, enormous progress has been made with elucidation of the molecular underpinnings of tumors of the central nervous system (CNS). Guidelines for how to build an integrated “histomolecular” diagnosis (eg, for diffuse gliomas) were published in 2014.¹ Indeed, in the revised fourth edition of the World Health Organization (WHO) classification of CNS tumors (2016), 3 major categories of diffuse gliomas in adult patients are now recognized based on the status of a few key molecular aberrations: diffuse astrocytic tumors, isocitrate dehydrogenase (IDH)–wildtype (WHO grade II, III, or IV); diffuse astrocytic tumors, IDH-mutant (WHO grade II, III, or IV); and oligodendroglial tumors, IDH-mutant and 1p/19q-codeleted (WHO grade II or III).^{2,3}

Because of this major restructuring, the traditionally used microscopic criteria for grading of diffuse gliomas are no longer sufficient. In 2016, the consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy (cIMPACT-NOW) was established to facilitate incorporation of novel, relevant molecular information into the clinical diagnosis and into future classifications of CNS tumors.⁴ Very recently, this consortium published an update stating that demonstration of epidermal growth factor receptor (*EGFR*) amplification, of telomerase reverse transcriptase (*TERT*) promoter mutation, and/or of combined gain of complete chromosome 7 and loss of complete chromosome 10 (+7/–10) in histologically lower-grade (WHO grade II or III), IDH-wildtype diffuse gliomas allows for a diagnosis of “molecular glioblastoma” (WHO grade IV).⁵

The armamentarium required to reach an optimal diagnosis for such diffuse gliomas has thus become more complex, and it is important to carefully select the assays used. Relatively simple and inexpensive techniques such as Sanger sequencing, fluorescent in situ hybridization (FISH), and loss-of-heterozygosity analysis can provide very valuable molecular information but have their shortcomings.⁶ More novel (and more expensive) next-generation sequencing (NGS) platforms allow for detection of multiple mutations in a single analysis, and increasingly for simultaneous detection of gene fusions

and chromosomal copy number aberrations as well. Very recently, genome-wide methylation profiling was reported as a very promising tool for CNS tumor diagnostics, providing not only a suggested diagnosis based on the methylation profile (including IDH-mutant versus IDH-wildtype nature of diffuse gliomas), but also detailed information on copy number aberrations (including presence/absence of *EGFR* amplification, complete or partial 1p/19q codeletion, +7/–10, and information on the methylation status of the O⁶-methylguanine-DNA methyltransferase (*MGMT*) promoter.⁷

In this issue of *Neuro-Oncology*, Bale et al report the results of a study comparing combined *EGFR* and IDH testing, *EGFR* testing based on IDH results, and no *EGFR* testing of diffuse gliomas and propose a “financially effective and clinically relevant test-algorithm” for recognizing histologically lower-grade, IDH-wildtype diffuse gliomas in routine clinical practice as “diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade IV.”⁸ In this algorithm, *EGFR* FISH testing is reserved for IDH-wildtype cases, but there is still a role for expanded genomic testing as, for example, histologically lower-grade IDH-wildtype diffuse gliomas without *EGFR* amplification but with *TERT* promoter mutation, and/or complete +7/–10 not readily identified.

An important asset of the study by Bale et al is that, using “real-world clinical data,” practical feasibility and financial considerations of molecular diagnostic testing of CNS tumors are taken into account. The relationship between (level of) acceptance, benefits, and costs is, however, complex. In its simplest form, one could argue that acceptance = benefits – costs. A test that scores relatively high on benefits and low on costs will more easily be accepted as a routine diagnostic tool, while an expensive test with very limited benefits will generally be considered as “not acceptable” (Figure 1).

The exact benefits of molecular diagnostic tests are, however, very difficult to measure. In fact, a clear framework for assessment of cost-effectiveness in this context is lacking.⁹ Ideally, a test not only reveals the truth, the whole truth, and

Fig. 1 Simplified representation of the relationship between benefits, costs, and (non)acceptance of routine application of molecular diagnostic tests. A test that scores relatively high on benefits and low on costs will more easily end up in the “acceptable” area (above the curve), while an expensive test with limited benefits will easily be considered as “not acceptable” (under the curve). For identification of “molecular glioblastomas” in the group of lower-grade, IDH-wildtype diffuse gliomas, testing according to the algorithm described by Bale et al.⁸ (asterisk in this graph) is less costly but also provides somewhat less information than can be obtained using, for instance, NGS or methylation profiling (MP; represented by a circle or square, respectively). Indeed, using this algorithm may help to increase the availability of clinically relevant molecular diagnostic testing. Obviously, in countries/centers with ample financial resources there is more room for acceptance of molecular diagnostic testing (curve shifted in direction of green arrow), and performing NGS or MP as a routine diagnostic tool may be within reach. The opposite is true for countries/centers with limited resources (curve shifted in the direction of the red arrowhead). Importantly, this graph concerns an oversimplified representation of very complex relationships, and the position of the curves and symbols are chosen quite arbitrarily.

nothing but the truth (so has perfect accuracy), but also allows guidance of patient management in a way that saves lives. But even when this is not possible (eg, in patients with a diffuse glioma), obtaining solid prognostic information can already be of huge benefit for a patient because therapeutic management can be optimized and will contribute to better quality of life. In other words, the benefit of (molecular) diagnostic tests ultimately lies in their effect outcome for the patients, and tests can have a positive impact on patient health not only by changing treatment decisions and improving outcome, but also by modifying “patient perceptions.”¹⁰

Limited financial resources form important impediments for worldwide implementation of especially the more expensive molecular diagnostic tools. The costs of such tools are determined by several components, including lab facilities with skilled personnel, equipment, and infrastructure, but also consumables that may be available only via commercial partners. There is quite a variability in costs for the same molecular tests across countries and institutions. Some of this can be explained by the way health care is organized (eg, based on market dynamics versus socialized medicine). Of note, there is a danger of being “penny wise, pound foolish” when refraining from using molecular diagnostic tools: Investing in a more precise diagnosis can save a lot of money later on in the life of a patient—eg, because costs and harmful side effects of non-efficacious treatments are avoided.

Further elucidation of the molecular underpinnings of CNS tumors occurs at a rapid pace and can be expected to allow for an even more precise and objective diagnosis of many of those tumors in the near future. Also, continued

development of technology along with reduced costs of diagnostic platforms brings state-of-the-art molecular diagnostics within reach of an increasing number of centers. Translating the increasingly refined histomolecular diagnoses into more specific and effective therapeutic approaches for patients suffering from glial CNS tumors is still lagging behind and remains top-priority. Meanwhile, it is important to design a framework for assessment of cost-effectiveness in order to keep the balance right between benefits and costs of (innovative) molecular diagnostics of CNS tumors.

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