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COMMENTARY

Brain Pathology

A *vade mecum* for crossing the second translational "valley of death" in brain tumor classification

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The road from a basic research discovery to widespread clinical implementation can be long. The journey has been said to involve three peaks and two intervening valleys (Figure 1) [4]. The first peak is the initial scientific discovery, typically made in a research laboratory and lacking immediate clinical significance. The second peak is the realization that a new scientific fact has clear medical significance, often following multiple correlative studies and sometimes a series of clinical trials. The third peak is creating the ability for a new clinical insight to achieve broad use to help patients equitably, which is enabled by national and international guidelines and resources.

Between each peak is a "valley of death" (Figure 1). The first valley is crossed moderately frequently and is a key aspect of translational work by pathologists. The second valley is traversed far less often since it relies on teams of people to develop practical consensus-driven approaches and to consider and generate the resources needed to accomplish implementation. The approaches to getting to the third peak have been termed dissemination and implementation sciences [5].

In tumor pathology, as in other clinical disciplines, many hundreds of novel correlations never make it into *standard* clinical practice. Those that do, with rare exceptions, do so via national or international processes. Notably, these processes have different foci and so a successful crossing of the valley requires their coordination.

i. World Health Organization (WHO): WHO has worked since the 1950s to generate a set of classifications to standardize tumor diagnosis around the world, including for central nervous system (CNS) neoplasms [6]. WHO classifications (Blue Books) aim to come up with clear, implementable definitions of tumor types. The earlier editions were nearly entirely definitions, with brief descriptions and scant illustrations, but more recent Blue Books are extensive textbooks in addition to collections of definitions. The Blue Books, however, have not historically guided reporting formats in surgical pathology nor do they necessarily detail diagnostic algorithms. The most recent CNS volume is the fifth edition, published in 2021 [7]. This edition was brought about during the COVID-19 pandemic, limiting the discussions underlying the decisions; it also had a distributed approach to editing, limiting its consistency. Nonetheless, the 2021 CNS WHO did advance molecular approaches in major ways, moving the field forward but creating more challenges for universal implementation around the world (see below).
ii. Consortium to Implement Molecular and Practical Approaches to CNS Tumor Taxonomy (cIMPACT): cIMPACT was established in 2016, following the updated fourth edition of the CNS WHO, to advance recommendations on CNS tumor diagnosis between WHO meetings [8]. WHO meetings can be rushed, with little time to have extensive discussions of the many key points; cIMPACT thus provides a forum to create more extensively debated recommendations for consideration at the next WHO deliberations.

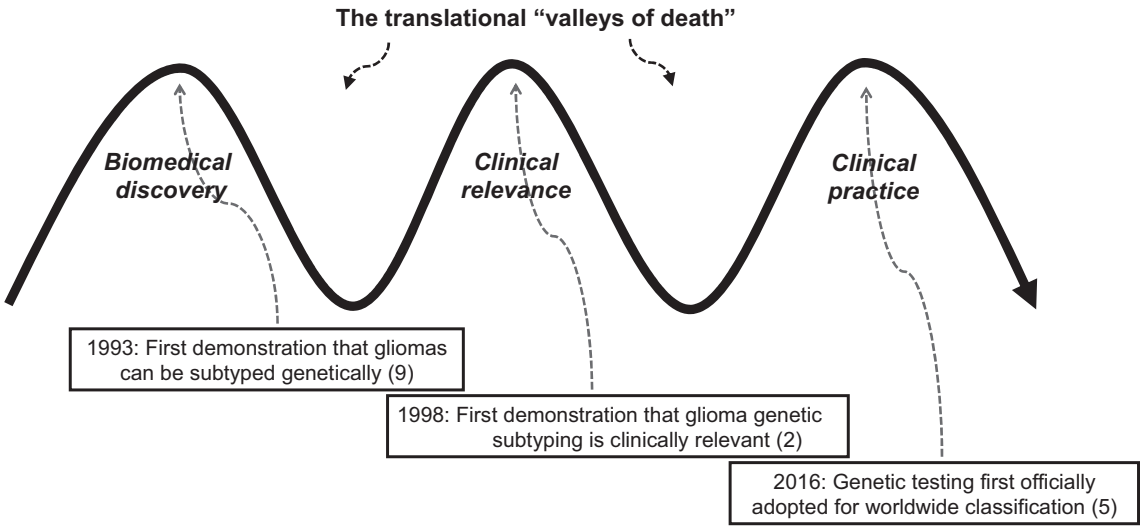

FIGURE 1 The peaks and valleys from biomedical discovery to standard clinical practice, with examples from glioma classification [1–3].

cIMPACT's seven guideline papers, published between 2017 and 2020, were largely adopted by the 2021 CNS WHO, showing its utility. Following the 2021 CNS WHO, cIMPACT has begun its next set of working groups to address questions brought about by further advances in the field.

iii. National societies: National societies such as College of American Pathologists, Royal College of Pathologists, and many others have played major roles in setting recommendations, mostly relating to diagnostic approaches and reporting. Within the context of individual countries or sets of countries, these initiatives set standards in highly effective ways and countries may mandate the use of society guidelines.

iv. International Collaboration on Cancer Reporting (ICCR): Reporting formats in surgical pathology have not been the province of the WHO nor have national societies closely harmonized their reporting formats around the world. Because uniform reporting is essential for standardizing approaches to clinical diagnosis and care, ICCR arose to coordinate the reporting recommendations of different organizations. The first CNS data set was published in 2019 [9] and a second is now underway.

v. Other initiatives: Despite the goals of the WHO to provide classifications for use across the globe, resource-limited countries have trouble implementing recommendations that are dependent on more expensive technologies. Two recent innovative initiatives aim to address this challenge. One, Adapting Diagnostic Approaches for Practical Taxonomy in Resource-Limited Regions (ADAPTRR), is sponsored by the Asian Oceanian Society of Neuropathology and aims to develop a surrogate biomarker approach to the 2021 CNS WHO, providing alternative, less expensive algorithms for diagnosis (personal communication, Drs Takashi Komori, Chitra Sarkar, and Vani Santosh). Two, St. Jude Children's Research Hospital, as part of their St. Jude Global program, plans to create centers capable of providing one-platform molecular analyses for pediatric tumors (personal communication, Dr. David Ellison), thus providing the actual resources necessary to implement the 2021 CNS WHO.

Despite the best of intentions, however, humans often create obstacles that get in the way, usually in the form of idiosyncratic approaches and adherence to sometimes arbitrary rules. For example, recommending the assessment of mitoses in measured microscopic fields (e.g., mm^2) rather than as ill-defined "high-power fields"—while eminently sensible from a scientific point of view and laudable as a goal—introduces a few practical challenges, creating an obstacle in the valley. In other words, when plotting a course, it is important to see the forest and not just the individual trees. An even more striking example of the difficulties of building consensus has been the recent generation of two separate international classifications in hematopathology [10]. In this sad situation, politics trumped [sic] long-term vision, creating needless complexity, controversy, and outright confusion that will persist at least until the next international classification effort (hopefully) rectifies this step backward.

Crossing the second translational valley for brain tumor classification thus requires not only that each

above initiative be successful, but also that they be coordinated in a balanced manner that keeps a clear view of the big picture… of the journey's destination. In this regard, plotting the pathway from biomedical discovery to standard practice cannot be done until enough evidence has mounted regarding the clinical significance of a discovery. At that time, the question becomes how to coordinate and align the people and organizations necessary to traverse the second translational valley. After more than 25 years of efforts to do so in international brain tumor classification, I believe success comes down to involving sensible planners and doers—people who must be both experts and diplomats. As such, I propose three overarching guides to involvement in these activities:

i. Consider how your decisions will affect the end users. The implemented system will be used by pathologists and oncological physicians, but most importantly it will influence patients directly. In the short and long run, the effects on patients are critical. Remember that this is not about your latest paper or review; this is about patients. This is not about your personal beliefs or anecdotal experiences; this is about peer-reviewed data and evidence. Working at implementation means functioning as a team to arrive at carefully considered, evidence-based decisions to help patients.
ii. Strive to see the forest from the trees. Individual truths may make complete sense in their immediate contexts but may not be universal. Just because something is true in one tumor type does not mean it is true in another. Biology is complicated. One must ask how individual pieces of evidence relate to other situations; secondary inferences should be taken with much caution. For example, for some markers, there may be widespread relevance across many tumor types, but for others, differences are greater than commonalities. Ignoring such differences can be a step backward, introducing problems that were not there before.
iii. Understand that you are only creating a "work in progress." No matter how hard and well a group works to generate a set of guidelines, biomedical knowledge grows and fields change, sometimes rapidly. What has been created today will eventually be viewed nostalgically by the current generation and may be viewed with humorous pity by the next generation. Nonetheless, creating the next "work in progress" is vitally important since it sets the stage for a new phase of clinical care and classification. But never imagine that your group is defining an inviolable truth.

As is evident from the above, my convictions are that individuals must work sensibly and boldly in collectives (and across more than one collective) to achieve successful national and international implementation. My hope is that the next generation of brain tumor experts will take these messages to heart as they strive to uncover new biomedical facts, explore their clinical relevance, and eventually translate these findings into standard clinical practice. They must be practical in how far each step can go; there is an old quip that to be 10 feet ahead of a parade is to lead a parade, but to be 10 blocks ahead is not to be part of the parade at all. But they must also be purposeful to aim their sights far ahead; as the intrepid explorer and travel writer, Freya Stark, said, "Surely, of all the wonders of the world, the horizon is the greatest."

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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