Comprehensive genomic profiling offers new insights for cancer diagnosis and therapy selection

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Advances in oncology research and next-generation sequencing (NGS) are expanding options for cancer treatment. NGS analysis allows researchers and pathologists to find variants that drive cancers and affect responses to therapies. Currently, comprehensive genomic profiling (CGP) NGS assays are able to assess hundreds of known cancer variants, helping physicians to better identify cancer types and deliver targeted therapies. However, CGP still has some challenges. The first challenge is that analysis requires expertise in both analyzing sequencing data and cancer biology. Another challenge is that the rapidly developing technology is not always understood by the agencies responsible for adopting diagnostic tools and/or determining reimbursement for service providers.

Dr. Csaba Bödör is Head of Molecular Diagnostics in the Department of Pathology and Experimental Cancer Research at Semmelweis University. He is also Group Leader for the Molecular Oncohematology Research Group at the Hungarian Centre of Excellence for Molecular Medicine (HCEMM). Dr Bödör and his team provide diagnostic services and expertise for clinicians, as well as substantive research information needed by agencies to evaluate CGP testing for implementation purposes. We spoke with Dr Bödör to get his insights on CGP testing in Hungary and the benefits of this technology.

Q: Can you tell us about the Department of Pathology and Experimental Cancer Research and your role there?

Csaba Bödör (CB): We are based at Semmelweis University in Budapest. This is the largest biomedical institution in the region. The department I work in is the Department of Pathology and Experimental Cancer Research, where I run the molecular

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diagnostic division with 20 to 25 people. We serve as a diagnostic center for more than 30 different clinics across the country, providing complex pathology services to multiple internal and external clinics covering all disciplines of oncology, including oncohematology, solid tumors, and soft tissue cancers. We perform routine surgical histology, immunohistochemistry, cytogenetics, flow cytometry, FISH*, and NGS, including CGP. In molecular oncohematology, we provide basic and molecular diagnostic services for external partners on close to 7000-8000 tests per year, and a similar number in solid tumors.

The Hungarian Center of Excellence for Molecular Medicine is my secondary affiliation. This is a large EU-based initiative where I run a translational research group in the field of B-cell lymphomas. We also recently received significant funding from the National Research, Development, and Innovation Office under the Hungarian Oncogenome Program that allowed us to develop custom NGS panels, invest in lab infrastructure, and generate CGP results well ahead of the reimbursement model in Hungary.

Our strategy was to launch a pilot project for 12 months to evaluate the value of performing CGP compared to a small panel or sequential testing strategy for all incoming samples. We analyzed close to 300 patients, including around 50 pediatric cases and 250 adult cases. Of course, there will be tumor types where CGP offers a lot of benefit and other tumor types where the knowledge is not mature enough to benefit from CGP, but it's something we need to try today in our search for the most practical applications of this type of testing.

Q: What benefits are you seeing for CGP over other methods?

CB: CGP is a great strategy compared to monogenic testing, or smaller panel approaches, especially when you are analyzing multiple different tumor types. With CGP, you have a universal cancer panel that covers the majority of known biomarkers, including tumor mutation burden, microsatellite instability, and all of the genes implicated in cancer oncogenesis and are potentially targetable. This is what I see as the main advantage for CGP, to have a universal test for virtually all cancer types that is capable of identifying biomarkers in potentially all genes that may be important and actionable.

* FISH: Fluorescence *in situ* hybridization

Q: How many genes do you currently assess with CGP?

CB: Our current panel has 500+ genes. It covers everything that we need for the cases we see as a center working with many different cancer types. We have also developed and used custom panels for hematological malignancies within the framework of the Hungarian Pediatric Leukemia Genomic Profiling Project in collaboration with the Hungarian Society of Pediatric Oncology.

Q: How does CGP testing help the patients?

CB: There are a number of cases where we were able to identify actionable genetic lesions that led to the application of targeted therapies. I would specifically point to pediatric sarcomas where we have identified several actionable gene fusions that led to successful application of *NTRK* inhibitors and other targeted therapies. In gynecological cancers, we have identified homologous recombination repair gene mutations in a considerable proportion of patients, in addition to *BRCA1* and *BRCA2* mutations, which led to application of PARP inhibitor therapies. We have also identified actionable fusions and mutations in lung, breast, and urothelial cancers. It is important to note that CGP is not only capable of identifying targetable lesions, but may also have influence on the diagnosis based on the presence of specific genetic markers, or it may predict resistance to certain therapies.

We work closely with our clinical partners and discuss the individual cases and reports on a molecular tumor board and the results influence therapeutic decision making in a subset of cases. It's becoming apparent that CGP should not be considered as a last resort, but should be performed earlier during the patient's journey.

Q: What is the the current role of CGP in oncology care?

CB: There are tumor types where a smaller targeted panel is reasonable and sufficient to address the clinically relevant questions. For example, we are not there yet to apply CGP for all non-small cell lung cancers. However, for pediatric tumors, for various sarcomas, and for tumors without standard therapy, we believe that CGP should be performed primarily. In these cancers, it is much more cost efficient to use a large CGP panel instead of other approaches. Nevertheless, as these technologies develop and become more affordable, a broader genomic characterization will be available for most patients. This is, of course, facilitated by the discovery of novel biomarkers and the development of targeted therapies.

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Q: How instrumental is NGS to the multidisciplinary tumor board?

CB: NGS data are of crucial importance to the information that the tumor board receives. The standard way of molecular testing in Hungary has been the monogenic sequential testing for biomarkers like *EGFR*, *ALK*, *ROS1*, etc. with different techniques. However, with the constantly increasing number of biomarkers to be tested, you need a panel approach and NGS is the way to go. It's a matter of debate whether you should focus on smaller panels or if our knowledge is mature enough to use CGP, but NGS clearly represent the preferred technology in molecular oncology. The multidisciplinary molecular tumor boards are instrumental in deciding on the appropriate tests and in defining the therapeutic strategy based on the available clinical and molecular data.

Q: Do you see monogenic approaches being phased out?

CB: Yes, slowly. For example, in Hungary, all of the laboratories are shifting to a 50-gene panel for non-small cell lung cancer because it is much more cost efficient to look at these 50 genes together with gene fusions instead of the monogenic sequential approach.

Q: What is the current reimbursement policy for CGP testing in Hungary?

CB: As of January 1 of this year, CGP tests are reimbursed by the National Health Insurance Fund of Hungary. Every case is discussed by the National Molecular Tumor Board and, following approval by this board, the test is reimbursed to the laboratories. Currently, Semmelweis University and the National Institute of Oncology are the two centers with license to perform CGP, however the number of centers performing this type of molecular profiling is expected to increase in the future.

Q: Where do you see CGP making the biggest difference in the future?

CB: NGS has already made a significant impact in the field of oncology and these technologies already represent the standard of care in some areas of oncology. My vision is that a broad genomic profiling will be a crucial part of the oncology workup at the beginning, before the actual treatment of these patients. What I anticipate is broad accessibility to these tests for all patients across Europe in the future.

However, when we talk about CGP, it is important to note that, although genomics does help a lot of patients, it is not the ultimate solution for all cancer patients. It brings solutions and it brings targetable alterations, but does not solve the cancer problem. We need to appreciate that the big picture is much more comprehensive, and understanding the immunological background, the transcriptome, and microbiome relations of the patient could give us the complete picture one day. Current testing is comprehensive in terms of DNA and RNA, but epigenetic changes, transcriptomic, microbiome, and metabolomics patterns and networks may represent the keys to the remaining secrets of cancer.

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How important is local support from GeneTiCA for your work?

CB: It is very important. We have developed a very good relationship with GeneTiCA. The flexibility, response, and speed of a local distributor can be very helpful. There is also an active relationship in terms of the IT background and data analysis. It works very nicely and having local support, whether it's the original manufacturer or a distributor, is crucial, especially in these difficult times with COVID when you can have a local stock generated by the distributor and you are not left short of needed reagents.

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