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Precision oncology in the Czech Republic

An expert perspective on NGS use in cancer care in Central Europe

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Advances in next-generation sequencing (NGS) have led to significant changes in how we understand cancer at the cellular level. Using NGS methods, researchers have cataloged a myriad of mutations that drive cancers, as well as variations that affect patient responses to therapies. This means that clinicians now have a greater understanding of tumor types and can potentially select therapies that may lead to better patient outcomes, offering new hope to current and future cancer patients.

Ondřej Slabý, PhD is a group leader at the Central European Institute of Technology at Masaryk University in Brno, Czech Republic. He is also Head of the Department of Biology for the Faculty of Medicine at the same university and Head of the Laboratory of Molecular Pathology at the Department of Pathology, University Hospital Brno. Prof. Slabý's team uses a range of NGS and molecular biology methods to increase precision oncology knowledge and to support clinicians in interpreting cancer patients' genomic findings. We spoke with Prof. Slabý about his role as an oncology researcher and molecular pathologist in the Czech Republic.

Q: What are some of the projects in your lab?

Ondřej Slabý (OS): We have a lot of projects ongoing in our lab, mostly focused on noncoding RNAs in solid cancer. One of the subprograms is focused on precision oncology, mostly in pediatric cancer—pediatric solid cancers, not leukemias or lymphomas. This is the project I really like because it has direct consequences for health care and we can see the results. In the precision oncology work, we focus mainly on the direct application of genomic findings, but we are also trying to develop new approaches, such as exploiting transcriptomes to find druggable information, and conducting epigenetic profiling.

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Another long-term project is looking at noncoding RNAs in solid cancers as biomarkers and potentially therapeutic targets. In terms of noncoding RNAs, we are focused mainly on microRNAs, where we have discovered and characterized some new microRNA oncogenes and tumor suppressors. We've also developed some tools for early cancer diagnostics from blood, serum, and urine.

Q: How does your lab use NGS for patients?

OS: Some of the information we get from sequencing has a direct impact on care for the patient. The findings with the highest clinical significance are usually obtained by whole-exome sequencing of tumor DNA and comprehensive analysis of gene fusions at the RNA level. We also get other complex information about the tumor biology, like transcriptome or methylome, which currently has no, or limited, impact on the care of the individual patient. Transcriptome information is used mainly for molecular classification of medulloblastomas and methylome for the precise diagnostics of brain tumors and sarcomas. However, this additional information is usually our basis for future research in cancer genomics. We also upload the data into public repositories for other scientists to work with, supporting analysis of large cohorts of patients.

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What is the role of research in patient care?

OS: The research is part of the whole paradigm of thinking about cancer therapy. One of the roles of precision oncology research is to generate the clinical evidence to support reimbursement for additional tumor-agnostic therapies. We do have a few examples of the drugs being registered independently based on the tumor origin, and getting reimbursement for things like NTRK or checkpoint inhibitors. The clinical evidence published in the scientific literature helps with the discussions with the health insurance companies. However, the precision oncology approach is not widely applicable because the costs will be significantly increased in comparison to current standards of care and no health care system in the world is ready to pay for it. So, there is a need for collaboration with big pharma and other stakeholders to find the scenarios and the mechanisms to think about reimbursement, like risk-sharing models. In a risk-sharing approach, the targeted drugs are initially paid for by the industry. If, after a predefined period, regular treatment and checkup results in a good patient response, then the treatment is covered by the insurance company. So, there are some models under discussion.

We also need some changes to enable faster and more rational registration of targeted drugs that are indicated based on the molecular findings of the tumor. The evidence-based approach with randomized trials, often of thousands of individuals, is not always applicable for this setting. We can do more in small precisely designed trials with drugs that are indicated based on the individual tumor properties. The paradigm is changing and is also currently the subject of wide discussions between all stakeholders, including regulatory bodies, policy makers, health care providers, and the pharmaceutical industry. It's great to be here and be part of it.

Q: How is comprehensive genomic profiling (CGP) used to find therapies for patients?

OS: CGP use is geographically dependent right now. Between countries, there are still differences with the availability of the targeted drugs indicated based on the CGP analysis. In fact, the biggest obstacle is actually the availability of the therapies. For example, we can use CGP and find a mutation, find a druggable target, and know that a MEK or EGFR inhibitor is the right approach for our patient. However, the problem is that the drug may not be available with the insurance coverage and it can be difficult for the patient to get the drug.

In the Czech Republic, our situation is quite good, at least in pediatric oncology. We can get coverage for the drugs for our pediatric cancer patients in about 80% of the cases where we identify some actionable mutation. In adults the situation is more difficult, with a reimbursement success rate ranging from 5% to 50% depending on the specific insurance company. In terms of technologies, we have five centers in the country providing CGP testing for a population of 10 million. Three of these centers provide only panel sequencing of selected genes and two centers provide more comprehensive testing, including whole-exome sequencing along with some additional methods to describe the biology of individual tumors.

Q: Is the testing different for pediatric cancer patients?

OS: In pediatric cancers, the testing situation is quite different. If you look at The Cancer Genome Atlas (TCGA), the number of cancers listed from the pediatric population is quite low in comparison to adult cancers. There are some special genomic databases for pediatric cancer patients like the one operated by St. Jude Children's Research Hospital, but the information for some rare cancers is still not sufficient.

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In comparison to the tumors of adults, pediatric tumors typically have a very low number of mutations. Therefore, to get a reasonable number of actionable findings in pediatric cancers, we must employ more comprehensive approaches beyond the panel sequencing that is commonly used in adult oncology. DNA analysis in the pediatric population, like whole-exome sequencing, is enabling us to get actionable information in about 25% to 30% of cases. In the remaining 70%, the output of the analysis is negative and there is nothing to be offered.

In terms of the RNA sequencing and transcriptomes, the situation is worse. We have a very good diagnostic yield of about 15% from RNA gene fusion analysis. We also know that there is actionable information in the transcriptomes from RNA sequencing. However, there are currently no bioinformatics approaches for exploiting the individual transcriptomes, or extracting this actionable information. This is extremely important for future research.

All of the data we generate are immediately used for diagnostics and the direction of therapies, and this data can be used for future research in pediatric cancer to identify new therapeutic targets, approaches, etc.

Q: Who does receive CGP testing?

OS: In our center, all pediatric patients with high-risk refractory solid cancers receive whole-exome sequencing, gene fusion, transcriptome, and methylome analysis and are discussed at a pediatric molecular tumor board. For adult patients who are recommended for testing by the institutional molecular tumor board, we use CGP with a combined DNA/RNA sequencing panel.

Currently, the indication criteria used by the molecular tumor board are not clearly defined. We have a nationwide project working on the definition and harmonization of indication criteria for CGP in adult oncology across all potential diagnoses, including pancreatic cancer, lung cancer, colorectal cancer, and breast cancer. There is also discussion around who should be the patients and who should be tested by and discussed at a molecular tumor board. For instance, should it be young patients with progressive disease and no other treatment options and good performance status? This is a common profile for patients currently presented at the molecular tumor board and who currently receive CGP testing in our center.

Q: Can you explain how the molecular tumor boards work in Czech Republic?

OS: The molecular tumor board is a standard, multidisciplinary committee at the hospital that discusses individual patients to find the best therapeutic approach based on the molecular findings of the tumor. At our center, we have two molecular tumor boards, one for pediatric cancer patients and one for adult cancer patients. Panel-based CGP is used for the adults and a more detailed CGP is used for children, but CGP is only available for patients preselected by the tumor boards and, as was already said, the indication criteria in adults are still the subject of discussions.

NGS is also used in routine molecular testing, independently from the tumor boards. For instance, in lung cancer where the number of targeted drugs and the number of the biomarkers to be tested have significantly increased in recent years, NGS is a logical approach. This is partly because with the increasing number of individual biomarkers, the cost of the NGS becomes lower than individual testing of biomarkers by other methods. Also, there is the limited amount of tissue available for testing. The path from this type of genomic testing to drug indication is straightforward and there is no need of tumor board discussion.

However, the number of patients referred for molecular tumor boards is increasing and, while we are capable of scaling to process thousands of samples at the level of laboratories, the tumor boards are limited in the number of patients they can review. This is something that will eventually impact wider implementation and that we have ongoing discussions about.

Q: How accessible is NGS testing for oncology patients in the Czech Republic?

OS: We have reimbursement coverage for NGS testing, so the access to testing is good. Actually, until recently, all of the funding for the NGS testing was from grant agencies and charities. Starting in 2021, we now have codes for reimbursement and insurance coverage for NGS testing of patients who are recommended by the institutional molecular tumor boards.

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Q: What benefit do you see from participating in the Illumina advisory board?*

OS: I really enjoy my participation on this advisory board because we know what our colleagues are doing in the US, Australia, and Japan from their publications, but it is always only a part of the story. To have a chance to personally discuss and exchange experiences is invaluable. It is only from discussion that you can confirm that your approach is right. You also see that your colleagues around the world face the same problems as you.

The advisory board was nicely straightforward. For example, when we were defining the most significant obstacles in the various approaches from a technological perspective we were asked what are the biggest issues in bioinformatics and what are the biggest issues in the various parts of the process? We have shared views in most cases because we face the same challenges.

Q: Where do you see NGS making the most impact in oncology in the next five years?

OS: I think that the future of cancer therapy will be based on two pillars. The first one is precision oncology and the second one is immunotherapy. The precision oncology approach is actually the only way, from my point of view, to switch from the lethal metastatic disease to the chronic disease category, the same as we did for HIV. Metastatic cancer cannot be cured completely, but the aim is to get it under control for enough years to allow the patient to die from a myocardial infraction in their 80s and not from the cancer. In the future, I believe that we will be successful with the treatment of the disseminated metastatic cancer with a combination of precision oncology, immunotherapy, and the usage of combined therapies based on the individual genomic findings.

The number of the targeted drugs is also continuously increasing. Therefore, the number of potential biomarkers to be tested is increasing. For practical reasons, it won't make sense to test all of these individual biomarkers individually. For instance, as we discussed, in lung cancer there is a limited amount of the tissue that we have for the analysis and this NGS approach enables us to get all of the information at once from one piece of tissue. Actually, compared to individually testing biomarkers by PCR and FISH, NGS is less expensive right now.

* This advisory board was organized by Illumina to gather feedback on market needs and trends, as well as opportunities and challenges for the adoption of whole-genome and transcriptome sequencing in routine testing of paediatric cancer patients.

I also believe that in five years NGS facilities will be part of all pathology departments, with the costs significantly below the current costs due to the huge amount of testing. This means that if we use NGS, CGP, and whole-exome sequencing for selected patients right now, in three to five years, I expect all tumors will be tested by NGS as part of the routine diagnostic process.

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