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How to move towards precision I-O? innovation in biomarker R&D

IMMUNO-ONCOLOGY INSIGHTS

SPOTLIGHT

INTERVIEW

Old data, new tools: leveraging routinely acquired patient data to address current challenges in I–O

Ròisin McGuigan, Editor, *Immuno-Oncology Insights*, talks to **Anant Madabhushi,** Professor of Biomedical Engineering, Emory University, and Research Health Scientist at the Atlanta Veterans Administration Medical Center.

ANANT MADABHUSHI is a Professor of Biomedical Engineering; and on faculty in the Departments of Pathology, Biomedical Informatics, and Radiology and Imaging Sciences at Emory University. He is also a Research Health Scientist at the Atlanta Veterans Administration Medical Center. Dr Madabhushi has authored more than 450 peer-reviewed publications and more than 100 patents issued or pending. He is a, Fellow of the American Institute of Medical and Biological Engineering (AIMBE), and the Institute for Electrical and Electronic Engineers (IEEE) and the National Academy of Inventors (NAI). His work on 'Smart Imaging Computers for Identifying lung cancer patients who need chemotherapy' was called out by Prevention Magazine as one of the top 10 medical breakthroughs of 2018. In 2019, Nature hailed him as one of five scientists developing "offbeat and innovative approaches for cancer research". Dr Madabhushi was named to The Pathologist's Power List in 2019, 2020, 2021 and 2022.

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Better predicting which patients will respond to checkpoint inhibitors remains a critical challenge for the I–O field. Biomedical engineer and AI expert Anant Madabhushi discusses how combining routine patient data with the power of computational tools can help to address the problem – and why he chose to take an 'anti-black box' AI approach.

Q Can you tell us about your background, and your new role?

AM: I am a biomedical engineer by training and by profession. I did my undergraduate work in biomedical engineering in Mumbai, India, then went to the University of Texas, Austin, and did my Master's, and then my PhD in bioengineering at the University of Pennsylvania. I landed a faculty position in biomedical engineering at Rutgers University straight out of my PhD, where I stood up a laboratory on computational imaging and personalized diagnostics.

In 2012 I moved to Case Western Reserve University, where I started the Centre of Computational Imaging and Personalized Diagnostics. I was there for a decade – and just a few weeks ago I joined Emory University as a Professor of biomedical engineering. In my new role I will be leading up an AI institute around health and medicine, and looking at developing and applying AI and machine vision technologies to address problems in health and medicine.

Q In your view, what is the current cutting edge in terms of imaging tools for cancer, and within that, how do AI, machine learning and computational tools fit into your work?

AM: That's a great question, and also a multi-dimensional one. Firstly, let me briefly discuss my own philosophy, and the way I think about problems. I'm a biomedical engineer, and therefore I've been trained to think translationally. When I approach problem solving, I am thinking from a deployment, clinical, and translational perspective. So while I'm certainly excited and intrigued by imaging technology, the bioengineer in me is always thinking 'what can we do with the data that we have at the moment?'

I am constantly trying to figure out how, with analytic and computational tools, we can derive the maximum possible information from routinely acquired data – CT and MRI scans, pathology images, and biopsy images. This data forms part of the routine clinical work-up for cancer patients, and is going to be available, by and large, across the globe.

> "...the bioengineer in me is always thinking 'what can we do with the data that we have at the moment?'"

There are a lot of exciting molecular-based technologies, single cell technologies emerging. We now have the ability to look at gene expression at an almost single-cell level with spatial transcriptomics. However, we must not forget that the staple for diagnosis continues to be what it has for the last hundred years or so: the standard hematoxylin and eosin (H&E) stained image. The big push for

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our group has been to develop and apply these computational analytical tools to interrogating routinely acquired pathology images such as H&E images, and see what we can accomplish.

I am fascinated by some of these technologies such as spatial transcriptomics, which will no doubt significantly further advance our understanding of the tumor immune microenvironment in particular. But from a practical and a translational perspective, I have to wear my biomedical engineering hat – there are opportunities to predict treatment response with the data that we are already collecting.

Q One area of your work is predicting response to checkpoint inhibitors – what tools and approaches are you using to identify patients who will benefit from these therapies, and what have been the most significant results of this work so far?

AM: Just in the last month we have published a series of papers [1–4] showing that using various machine vision and computational AI tools, we can start to interrogate the immune architecture of biopsies from routine H&E images. Patterns of immune architecture as characterized by machine vision and computational tools allow us to extricate measurements that then are associated with clinical outcome and objective response, in the context of cancer patients being treated with immunotherapy.

We have demonstrated this in the context of both gynecologic cancers, non-small cell lung cancer and head and neck cancer patients [5]. These patterns and features of immune cell architecture from routine H&E images allow us to predict which patients are going to respond to immunotherapy. We have also shown an association with longer-term outcomes including survival. Another encouraging finding was that the patterns were not limited to a particular immunotherapy agent – we could demonstrate the association with response and outcome across multiple different checkpoint blockade agents including atezolizumab, pembrolizumab, as well as nivolumab. That was really exciting, and again demonstrates the utility of routinely acquired data for addressing some of these problems in I–O.

Aside from the work we have been doing with biopsy images, there is a lot of information that resides in routine radiologic images as well – CT scans, for instance. Therefore, we are also using machine vision and AI tools to extricate information from CT scans, again to be able to predict response. We are looking at patterns of texture of the tumor as well as the surrounding tumor microenvironment, and also other patterns. For instance, our group made a discovery of features relating to the tumor-associated vasculature – patients that tended to have a better response also tended to have a much smoother tumor-associated vasculature. Patients who tended to do worse had a much more twisted and convoluted tumor-associated vasculature.

Q How do you plan to further translate these findings?

AM: As a biomedical engineer I'm constantly thinking about deployment and how to translate and move this forward into clinical practice. With that in mind, one

of the first things that was critical to demonstrating the feasibility of these approaches was to validate the algorithms in terms of retrospective, completed clinical trials. There have been a number of papers published showing the utility of AI for institutional data sets, but we wanted to go above and beyond and validate it in the context of completed clinical trials, because clinical trials represent the gold standard. In the clinical trial data set for CheckMate057, we were able to demonstrate that these features were able to predict objective response in lung cancer patients treated with immunotherapy [6].

In a study looking at CT scans in stage 3 lung cancer patients, we were able to demonstrate that patterns of the texture of the tumor and surrounding microenvironment were strongly associated with response in non-small cell lung cancer patients who were treated with radiation therapy as well as durvalumab, an immunotherapy agent from AstraZeneca [7].

The next logical step for this work is no doubt going to be prospective deployment. We are gearing up for this and actively working on ways in which we can start to move these algorithms into prospective clinical trial deployment. Then we can start to couple this within a clinical trial, where these algorithms could then be used to figure out, for example, whether a patient should be getting combination immunotherapy versus immunotherapy alone.

I am stating the obvious, but current biomarkers such as PD-L1 are just not very accurate. I think we all readily acknowledge that, and there is no debate there. One of the things that our group has started to investigate is if we look at low PD-L1 and high PD-L1 patients, what kind of additional value can these imaging-based biomarkers bring to the table? That has been some of the most exciting work that we've published recently [8,9]. Patients who have low PD-L1 are either unlikely to get immunotherapy, or if they do, are going to get immunotherapy in conjunction with chemotherapy. High PD-L1 on the other hand means patients are likely to get I–O monotherapy. Our work has found that even within the low PD-L1 setting, our imaging biomarkers are able to better stratify patients. We were able to find subsets of patients who were likely to do well even if they have low PD-L1. This is important from a translational perspective, because it suggests that this subset of patients could be candidates for I–O monotherapy, and might potentially avoid chemotherapy. It is also important from a patient-centric perspective, from a physician's perspective, and from a payer's perspective. If you can avoid chemotherapy in these patients without compromising patient outcome and response, and also avoid deleterious side-effects from a bout of chemotherapy, that is a big win.

Q Outside of your own work in this space, are there any other tools or approaches that are showing promise for you?

AM: There has been a lot of work from other groups in the AI space on predicting mutational status, trying to predict pathways, and ultimately predict the underlying molecular biology of these tumors. For example, the ability to predict the PD-L1 expression of a tumor based an H&E imaging or based on a CT scan, and then being able to predict the appropriate treatment. That is also a very compelling direction.

Spatial transcriptomics and the interrogation with new, higher throughput molecular-based profiling technologies are also exciting. The question will be how we make more sense of the

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data that we are generating. It is one thing to generate all that data, but what kind of markers and features can we prise out that would allow us to create better predictors of treatment response? This is a little bit of an unknown, but certainly the technologies are getting very compelling and really pushing the envelope of what we are able to study in terms of the immune milieu of these tumors.

"Being able to provide the interpretability associated with this decision-making will really help physicians, and will ultimately help convince patients as well."

On the imaging side, we continue to work towards better imaging. While a lot of our own work has been on routine standard diagnostic CT imaging, the fidelity and improvements on non-invasive radiologic imaging continues. It's the old adage: the better the imaging, the better the image processing. The better the imaging, the better the AI. As we potentially start to get better and better non-invasive imaging, it will in turn benefit the AI tools that we are developing, and we will be able to pull out more information from higher fidelity, better resolution imaging.

Going back to AI, there is a lot of work going on in the deep learning space, and novel algorithms for performing AI and machine learning. Deep learning is a class of unsupervised feature generation approaches, and combining feature engineering-based approaches with deep learning approaches could be very compelling. Our approach has been a little different to others in the space, as we have taken a more interpretable, or what we term a hand-crafted, approach.

Q Why was taking a hand-crafted approach important?

AM: We really want these approaches to be interpretable. Ultimately we are looking for these approaches to be clinically deployed, and a big part of that is to make sure that the physician using these tools truly understands how these technologies work. If you consider a physician who has to make the decision about who should be getting immunotherapy and who should not, that is a big decision. Just being able to look at the prediction may not be compelling or convincing enough for the physician; she or he will want to understand how that decision was arrived at. This is where having intentional interpretability built in becomes really important, and distinguishes what we are doing from the more 'black box' approaches. We have taken the 'anti-black box' approach, if you will. We are thinking from the regulatory aspect, the adoption aspect, and from a patient perspective as well. A patient will want to know why their doctor has decided against chemotherapy. Being able to provide the interpretability associated with this decision-making will really help physicians, and will ultimately help convince patients as well.

Q What will be your own goals and priorities within the next couple of years?

AM: The work that we've done over the last decade at Case Western, and prior to that the work that we started at Rutgers University – plus all the parallel developments that have been happening in the areas of AI and machine vision – have brought home the message that there's a huge opportunity to take advantage of routinely acquired data with these tools.

I am also very passionate about global health and health disparities – these are two areas where I see a real opportunity to make a difference. We need to think about what the lowest common denominator is when it comes to the data that can really benefit not just patients in North America or Europe, but across the globe – particularly in low- and middle-income countries. Having grown up in India myself, there is a certain attachment for me, and a need that I feel has to be addressed. Global health is something that I think about a great deal, and how we can bring these tools and start to apply this to the greatest possible population.

The other area is health disparities – I don't think we have done a good job in being able to address application of novel technologies in diagnostics, prognostics, and treatment response prediction across diverse populations. We have to acknowledge that in particular, underrepresented minority groups have not fully benefited from these technologies. If you take risk stratification assays that are now available for women with breast cancer as an example, data has come out showing that those risk calculators to identify which women have more aggressive breast cancer versus less aggressive breast cancer don't work well in African American women. This is because when they were developed they were not exposed to a significant proportion of African American women, and were instead primarily exposed to women of European ancestry. We know that there are biological and disease-specific differences across different populations. The opportunity with AI and machine vision is to try to understand what these differences in disease phenotype are across different populations, but then also to go beyond that and start to create more tailored, population-specific risk models for different populations, so that we have more equitable deployment and application of these assays.

If I had to pick two things I want to really focus on over the next 5 years, I would say it's the health disparity aspect and focusing on equitable AI, but then also thinking about how we can deploy these tools in a global context.

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AFFILIATION

Dr Anant Madabhushi
Professor of Biomedical Engineering, Emory University
and
Research Health Scientist, Atlanta Veterans Administration Medical Center

AUTHORSHIP & CONFLICT OF INTEREST

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HOW TO MOVE TOWARDS PRECISION I-O?
INNOVATION IN BIOMARKER R&D

SPOTLIGHT

INTERVIEW

Taking the initiative to advance precision medicine: a perspective from Norway

Ròisin McGuigan, Editor, *Immuno-Oncology Insights*, **talks to Kjetil Taskén,** Professor of Medicine, University of Oslo & Head, Institute for Cancer Research, Oslo University Hospital.

KJETIL TASKÉN (born 1965, MD, PhD) was appointed Professor of Medicine at University of Oslo (UiO) in 2001 and has since 2018 served as Head of the Institute for Cancer Research, Oslo University Hospital (OUH) where he is also Group Leader for the Cell Signaling and Immune Regulation Group (approx. 20 people) in the Dept. of Cancer Immunology. He was the Director of the Biotechnology Centre of Oslo, UiO from 2003 to 2016 and the founding Director of Centre for Molecular Medicine Norway (NCMM), Nordic EMBL Partnership, UiO where he served from 2008 to 2018. He established and directed the national infrastructure for academic chemical biology and drug screening (Nor-Openscreen, coupled to EU-Openscreen) and was the national director for EATRIS (translational medicine). More recently he has been key in building the national cancer precision medicine initiative for Norway (InPreD molecular diagnostics infrastructure, IMPRESS-Norway national clinical trial and CONNECT public-private partnership) and is Director of the OUH Centre for Precision Cancer Medicine. He is a partner in the K.G. Jebsen Centre for B Cell Malignancies. He has served or serves on a number of evaluation panels, SABs and Editorial Boards, including ERC StG panel LS3 (2014-20), the IMI Scientific Committee (2017-22), and Cancer Research UK New agents committee (2019-). Taskén received the Anders Jahre Medical Prize for younger scientists in 2002 (Nordic award), and won the King Olav V's Prize for Cancer Research (national life-achievement award) in 2016. He was elected to the Norwegian Academy of Science and Letters in 2005. Taskén is author of >290 publications and inventor > 20 patents (>14,000 citations, h-index =62). Current research is in tumor immune evasion mechanisms and immune regulation and in functional precision medicine and drug screening for different solid and blood cancers.

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What does the practical implementation of precision medicine in oncology look like, and how can key public and private stakeholders be brought to the table? We spoke to Kjetil Taskén to find out how Norway is driving precision medicine in cancer through three nationwide initiatives, and to discuss his own work on functional precision medicine and tumor immune evasion mechanisms.

Q Can you tell us a bit about your background and current work?

KT: I am a medical doctor by training, and a professor of medicine at the University of Oslo. I have been involved in research since medical school. I was director of the Biotechnology Center of Oslo, and the founding director of the Center for Molecular Medicine Norway at the University of Oslo until 2018. I am currently the Director of the Institute for Cancer Research at Oslo University Hospital, with a research group in our Department of Cancer Immunology. My research is mainly in two areas: the first is tumor immune evasion mechanisms, and the other is precision medicine – particularly functional precision medicine, including drug screens and functional methods that will add to and complement genetic and transcriptomic analysis.

I have been doing strategic work over the last five years to organize a precision cancer medicine initiative for Norway [1], and we are also setting up a center for advanced cell and gene therapy.

Q What challenges or gaps in care was the precision cancer medicine implementation initiative for Norway developed to address?

KT: I chaired a strategic working group looking at the obstacles and bottlenecks to implementing precision cancer medicine, and we wrote a report that highlighted three things that needed to happen to get precision medicine going in the cancer area.

Individual pathology departments previously performed small gene panels and individual genetic tests, but not big gene panels or organized next-generation sequencing for cancer patients. We therefore needed to get molecular cancer diagnostics going to be able to stratify patients into clinical trials, and to start recruiting clinical trials using precision medicine to Norway. In parallel, we wanted to see if we could move some of this into ordinary healthcare.

We started working to make these things happen in the national arena, and organized two national meetings: one in summer 2019 to discuss how to organize the diagnostics, and one in January 2020 to prepare the launch of a big clinical trial for Norway.

The Ministry of Health in Norway very much wanted precision medicine to happen, and instructed the Norwegian healthcare systems and the regional and individual hospital trusts. We worked to organize this from the bottom up, whilst trying to align with the authorities and maintain a good collaboration with the Ministry and regional healthcare trusts. They released money to get the diagnostics going and to set up a clinical trial. They also organized for gene panels to be reimbursed by the healthcare system to stratify patients into clinical trials, and reimbursement on drugs in our clinical trial in defined settings and for patients that respond.

All of this work led to setting up InPreD-Norway (Infrastructure for Precision Diagnostics for Norway), which is led by Oslo University Hospital. This also involved setting up a national molecular tumor board. It was laid out that there would be a three-tiered system, with two of

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the biggest university hospitals doing whole genome sequencing and large gene panels. The other four university hospitals would also move to big gene panels and take on part of the load of diagnostics, and local pathology departments across Norway would do smaller gene panels.

We got everybody on board with the message that we needed to have a few common priorities rather than many individual priorities – this is about doing something for patients, not to market individual hospitals or people. To this end, we have not had authors and hospital logos on central documents.

Next, we set up a national clinical trial: the IMPRESS-Norway Trial [2]. The first eight drugs came from Roche, and the next four from Novartis. We also have Incyte, AstraZeneca, and Eli Lilly on board. We now have 16 drugs, which will hopefully increase towards the end of the year. The more drugs in the algorithm, the better the overall effect of a precision medicine approach.

All of this is now scaling up in Norway – but is not perfect yet, as we need to increase patient access. The aim is to scale up to six university hospitals running the big gene panels. We are using the TruSight Oncology 500 assay from Illumina at the moment. The goal is that all patients with advanced disease will have the opportunity to receive testing with large gene panels and get advanced molecular cancer diagnostics. We will then move towards getting this to patients earlier. In addition, IMPRESS-Norway has projects with Roche/Foundation Medicine and Illumina on testing analysis of circulating tumor DNA in parallel with the InPreD diagnostics.

The third initiative is the CONNECT public-private consortium [3]. We built this around the other initiatives in order to work more closely with industry. We spent about a year setting this up in a project group with three pharma companies, Oslo University Hospital, Oslo Cancer Cluster, and the Norwegian Pharma Industry Association. This included establishing four working groups: one for diagnostics, one for clinical trials (particularly the IMPRESS-Norway trial), one for health economy and reimbursement mechanisms, and one for legal and data access.

We worked out a framework agreement to allow a public-private partnership with membership fees which would be the same for private and public partners. The pharma group then recommended membership to their colleagues in other pharma companies, and we recommended to other hospitals and other public stakeholders. The Norwegian Cancer Society and the Norwegian Pharma Industry Association, The Norwegian Medicines Agency, The Norwegian Directorate of Health, and the Norwegian Institute of Public Health participate as observers while Oslo Cancer Cluster hosts CONNECT.

One challenge was how to have roundtable discussions and interactions without violating the principles of InPreD being a public infrastructure for diagnostics and IMPRESS Norway an investigator-initiated trial. Companies cannot instruct an investigator-initiated trial, so we wanted to gain and give insight to public and private partners in CONNECT and be open for discussion whilst also respecting the fact that CONNECT cannot instruct the other initiatives. It also took work to establish how to bring the different partners to the table to discuss health reimbursement mechanisms, while respecting that people have different positions.

"The goal is that all patients with advanced disease will have the opportunity to receive testing with large gene panels and get advanced molecular cancer diagnostics. We will then move towards getting this to patients earlier."

A key to this was that we established an agreement to handle conflicts of interest and ensure we are not violating these principles. It was approved by the parties, and we decided that to be a founding member you had to sign up by a certain date, like for a book-building process in a share issue. We had 22 partners sign by December 20, 2020 – 12 pharmaceutical companies, six university hospitals, the Institute for Public Health, the Norwegian Cancer Society, the Norwegian Pharma Industry Association and Oslo Cancer Cluster as the host. We have also had more institutions join since who are not founding partners, so CONNECT now has some 30 members. It has been a dynamic and popular forum that works well, with a lot of discussion and interaction.

Q Why is public-private collaboration so important for driving precision oncology?

KT: Individual pharma companies who want to get into precision medicine face the challenge of finding patients. To find patients, you need access to hospitals or a national health care system that performs advanced molecular cancer diagnostics, including for very rare mutations.

Since we have reimbursement of the testing, we will have the opportunity to screen 2,500 patients per year, moving up to potentially 10,000 patients a year. Unless you are a company like Roche that has Foundation Medicine and can do this, it is going to be difficult to find patients. There is a need to make alliances with healthcare systems that can perform the screening, and the screening must be covered, because individual companies cannot pay to screen tens of thousands of patients to find ten for their drug.

From the public perspective, if you want to run a precision medicine trial you have to have drugs from different companies, and a molecular tumor board to make the optimal selection for the patient based on the diagnostics. So this is something that both the public and private side require in order to move forward.

It is beneficial for the industry to get their drugs tested, particularly on rarer indications, which provides real potential for market expansion. It is a win for the public side because they gather evidence in terms of what should be reimbursed, or not. It is a win for patients because they get access to drugs earlier, particularly for patients with rarer diagnoses and fewer lines of treatment available to them.

Q What have been the most significant results so far, and what are the next steps?

KT: We have run the diagnostics and national molecular tumor board for over a year now. We started operating in April 2021, and we have screened ~400 patients since then. We can find a drug in the IMPRESS-Norway trial for ~25% of patients. As we get more drugs, that may increase. However, as we screen more patients, it may instead decrease, because we now perform a preselection of the patients that recieve the diagnostics.

For an additional 15% or more of patients we either find another trial for them to be referred to, or we find an early access program for patients to receive further treatment. Their diagnosis may also be revised based on molecular diagnostics; and the patient therefore receives another treatment line in a different standard of care program. In total, around 40% of the patients

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receive an additional drug. The Drug Rediscovery Protocol (DRUP) in the Netherlands finds a drug for about 50% of patients, but they perform more prescreening.

Looking at the aggregated data, in the 25% of patients who get a drug in the IMPRESS-Norway trial, and in the 70 patients that have so far gone beyond the endpoint of 16 weeks, about 40% of the patients have stable disease or a partial or even complete response.

Q How would you define the current state of play in terms of discovering and developing reliable markers of resistance and response in solid tumors?

KT: There is a lot still to be discovered. As we run these big gene panels, and utilize transcriptomics and other things such as in the InPreD Diagnostic Network and the IMPRESS trial, we get whole genome sequencing sequentially, several times. This is a huge opportunity to find more things that are coupled to resistance to treatment.

There are also interesting opportunities to find more complex biomarkers, such as genes that are upregulated or mutated. Areas of interest include homologous recombination deficiency (HRD) genes and how they correlate to patient response to PARP inhibitors.

It will be the same in the I–O domain, with increases in understanding of who responds to different types of current or future immune therapies, and what makes tumors cold or hot. There is much still to be found out, and there are other modalities to be added, including protein biomarkers, flow cytometry biomarkers for hematology, and other more advanced approaches made possible with proteomics.

Then there is the domain of functional precision medicine. My lab has done a lot of work in drug sensitivity testing with live patient cells, which is more complex, but is also moving towards application. We think there will be additional types of biomarkers or readouts that will advise on clinical treatment decisions in the future. We need to build this into initiatives like the Norwegian Precision Medicine Initiative, in order to have new iterations of trials and bring in new diagnostics.

Q How could AI and machine learning tools be used potentially to integrate biomarker data? What is practical – both now and in the future?

KT: It is practical to integrate and look at more complex biomarkers. It will be interesting to see how we can model combined treatments and understand the synergy of which treatments positively add on to each other. More importantly, being able to predict which treatments work well in combination without testing them would be greatly beneficial, because you cannot test every combination.

In future, it could be that with all the molecular data and biomarker information you can gather about the patient's cancer, you could predict the optimal combination of drugs to treat that particular cancer earlier, and hit hard right away. This would be more effective than exposing the patient to the same drugs serially and making them resistant to each one in turn. I believe there are great opportunities in the future to get in earlier with this type of approach.

Q Are there any other tools or technologies showing promise in the prediction of resistance/response?

> "We need to see the same in immunology – functional immunology tests to see the tumor immune evasion mechanisms that are active in each patient's tumor."

KT: I am very interested in functional precision medicine, including drug testing and screening. We need to see the same in immunology – functional immunology tests to see the tumor immune evasion mechanisms that are active in each patient's tumor. There will be things that are specific to each type of tumor. There will also be things that are specific to each patient and that patient's immune history and immunogenetics.

One current area of study is response to immune checkpoint inhibitors. Some patients respond wonderfully, and others do not. Even if you combine two immune checkpoint inhibitors, you can only cure around 25–40% of patients, with a response in up to 60%. That means that 40% of patients are not responding. How do you find the ones that will respond, and what is happening in the other patients? What type of tumor immune evasion mechanisms do their tumors engage, and can we turn those mechanisms off? To answer these questions I think we need functional screens for tumor immune evasion mechanisms. I want to see this domain develop, along with diagnostics to complement what is in the pipeline.

We're seeing more engineered approaches that improve the immunity of the patients, such as CAR–T cells, and engineered cells that have T cell receptors (TCRs) rather than CARs, that have higher affinity. We will also see other engineered vaccine responses, but again, we need the diagnostics to develop in parallel.

Q What will be your own chief goals and priorities over the next five years?

KT: We are working on the Norwegian Precision Medicine Initiative and we want that to continue to develop, including new biomarkers and new diagnostic modes. We want to develop the trial we have now, as well as recruiting other trials with different designs, and move forward in the treatment lines.

We are also starting a functional precision medicine approach to stratify patients into trials., and my own lab is working on tumor immune evasion mechanisms. To further progress precision medicine approaches, we – or others – need to come up with the diagnostics and methods to functionally stratify patients into different treatments.

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AFFILIATION

Kjetil Taskén
Professor of Medicine
University of Oslo & Head
Institute for Cancer Research
Oslo University Hospital

AUTHORSHIP & CONFLICT OF INTEREST

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FASTFACTS

Leveraging oncology gene expression signatures to accelerate research

Sarah Church, Senior Scientist, NanoString Technologies

RNA signatures are at the forefront of cancer research and are used to enhance study outcomes and accelerate the translation of findings from bench to clinic. NanoString provides a range of innovative oncology solutions, including RNA expression signatures that span immuno-oncology, breast cancer, and lymphoma.

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SIGNATURE & ANALYSIS OPTIONS

A number of panels with clinically, analytically, and biologically established signatures are available, including the PanCancer IO 360™ panel, the Breast Cancer 360™ (BC 360) panel, the RUO Lymphoma Subtyping Test (LST) CodeSet, and the RUO PAM50 CodeSet. All panels have the ability to spike-in 55 genes of interest. These signatures can be used to vastly improve the statistical power and interpretation of data.

Signature data analysis services (DAS) by experts in nCounter data can expedite research, including full analysis reports **(Figure 1)**. These reports can distil large amounts of data into actionable signatures and provide publication-ready figures in a customizable way.

THE 360 SERIES

The 360 series is designed to give a holistic view of the tumor, tumor microenvironment, and immune response, with customizable options for the addition of genes.

The PanCancer IO 360™ gene expression panel contains 770 human genes in total, profiling the tumor, microenvironment, and immune response. It contains 48 biological signatures, including the Tumor Inflammation Signature (TIS) which measures activity known to be associated with response to PD-1/PD-L1 blockade therapy. The other 47 research signatures focus on biological themes such as tumor immunogenicity, inhibitory tumor mechanisms, anti-tumor immune activity, stromal factors, inhibitory immune signaling, and immune cell population abundance.

The BC 360 bulk gene expression panel contains 48 signatures across 13 categories measuring biological variables crucial to breast cancer tumor biology. Validated signatures in the report include PAM50 subtypes, Risk of Recurrence (ROR) and the Tumor Inflammation Signature. Additional research signatures focus on areas such as triple-negative breast cancer (TNBC) or Claudin-Low subtyping, signaling pathways, and tumor immunogenicity.

In order to expedite analysis to insight, 360 data analysis reports provide easy data interpretation, publication-ready figures and statistical outputs, as well as a consultative report out with a scientist. A summary of the attributes of the 360 series is given in **Figure 2**.

The 360 data analysis reports contain a customizable selection of response, grouping analysis, or survival analysis tailored to customer needs. Analysis outputs cover differential expression, survival analysis, and analytical plots.

Figure 1. Signature and analysis options and key benefits.

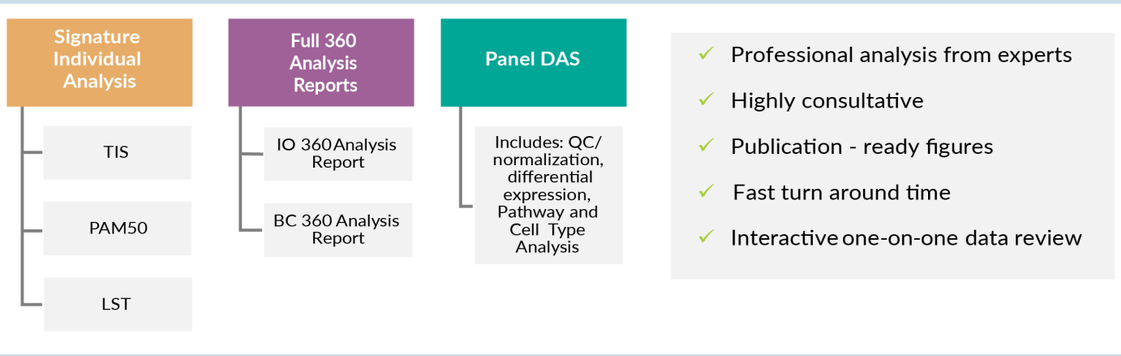
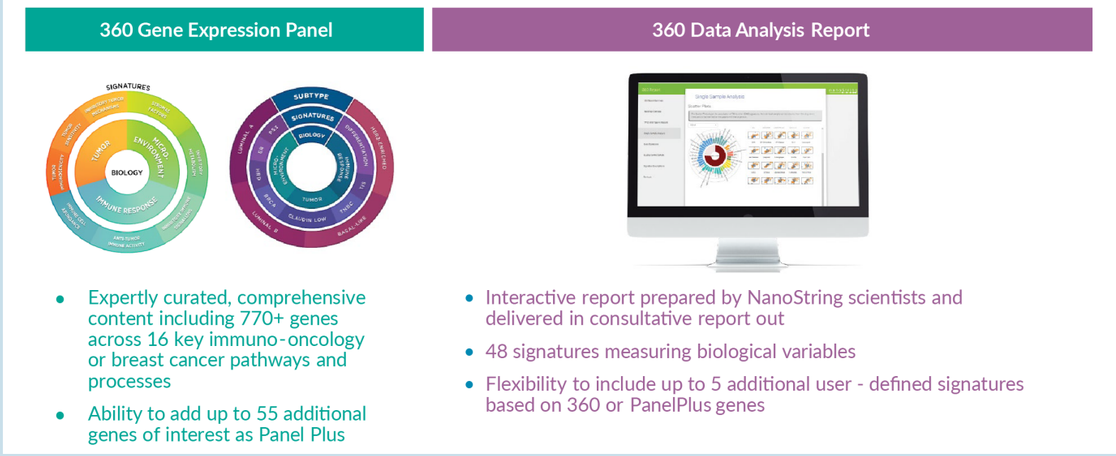


Figure 2. 360 Panel and data analysis reports allow discovery and validation of novel biomarkers and signatures.



BUILT-IN BIOINFORMATICS

NanoString panels have bioinformatics built-in. In the design of each panel, foundational scientific framework was leveraged and integrated with state-of-the-art knowledge of the biology. Research community resources were engaged in the development of simple and powerful data analysis tools.

ADDITIONAL ANALYSIS SERVICE OFFERINGS

For deeper insights, DAS scientists can use nSolver™ analysis software to provide advanced statistics and robust visualizations from any nCounter panel data.

Find out more Information about LST, PAM50, TIS and 360 signatures and access IO 360 and BC 360 demo reports

Email us for more details on accessing NanoString's Data Analysis Services: support@nanostring.com

IMMUNO-ONCOLOGY INSIGHTS

In partnership with: nanoString