

AN IN-HOUSE HOME FOR PRECISION ONCOLOGY

THE BENEFITS OF KEEPING MOLECULAR
TESTING IN-HOUSE, AS VIEWED
BY EXPERTS FROM AROUND THE GLOBE

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INTRODUCTION

Targeted and immuno-oncology therapies requiring biomarker testing have proliferated in the last decade, bringing hope to many oncology patients. Although molecular pathology is still relatively new, it's developing fast – no longer just the province of academic medical centers, but a discipline on its way to becoming routine practice. As a result, many healthcare providers now face a difficult decision: whether to outsource this new testing to centralized laboratories or implement it in their own. The issue has been hotly debated. What is best for the system – and what is best for patients?

This debate is vital for the future of both pathology and the patients themselves – and so, over year 2020, we have conducted a series of interviews with experts in the field and hosted a virtual panel debates now available to view on demand. It has been a great privilege to speak to experts from different countries, all with different – but extensive – experience and all united in their passion for their patients and for their discipline. In this e-book, we present the collected articles and the highlights of the panel debate.

It was fascinating to see, that across the globe, these experts agree on the same key benefits of “in-house” testing, which can improve patients’ treatment outcomes:

1. It significantly faster and so allows for fast and most optimal treatment decisions
2. It is much more “tissue saving”, allowing for possible future testing if required
3. It improves care coordination among multidisciplinary teams leading to true flexible personalized medicine
4. It enables local expertise development which will be required in this field as precision medicine, driven by biomarker testing is the future

We have also invited Garret Hampton, President of Thermo Fisher Scientific’s Clinical Sequencing Division, to share a few words. His team of pioneering scientists and experts have spearheaded the development and democratization of next-generation sequencing, a technology that has fueled research in precision oncology and will play a key part in its broad implementation for patients...

But that’s not all. We would also like to hear from you! Where do you stand on the role of precision medicine in patient care? Should molecular testing be conducted in-house or sent to a centralized laboratory – and why?

To share your thoughts, please contact:

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PRECISION ONCOLOGY GENOMIC PROFILING: IN-HOUSE OR CENTRALIZED?

An expert panel discussion



Targeted and immuno-oncology therapies requiring biomarker testing have proliferated in the last decade. Healthcare providers now face a complex decision: whether to outsource this new testing to centralized laboratories or implement it in their own labs. What is best for the system – and what is best for patients?

To explore these questions, we invited expert pathologists Fernando López-Ríos from Spain, Ruthy Shaco-Levy from Israel, Michael Vieth from Germany, and clinical scientist Philip Bennett from the UK to a panel discussion to share their views and experiences. They've participated in broadly different approaches to the issue, from limited testing hubs within a single country to plans to completely outsource testing to overseas commercial labs.

The discussion was moderated by Michael Schubert, editor of The Pathologist, and Luca Quagliata, head of medical affairs for Thermo Fisher Scientific's clinical sequencing division.

What does in-house testing mean to you when it comes to oncology?

RS-L: Performing all the pathology assays in my lab, from the hematoxylin and eosin (H&E) stain to the immunohistochemistry and molecular tests, is what appeals to me about in-house testing. It means correlating the molecular analysis with other clinicopathologic features to see the whole picture. For example, in breast cancer, we report on tumor size, tumor grade, and receptor status. For consistency and efficiency, molecular pathology should be included in that report – and performed on site.

FL-R: In-house testing means controlling the whole testing workflow so that you can influence turnaround times and other critical factors. In my opinion, it also enables us to put patients at the heart of the care process.

What is your institution's approach to precision oncology testing?

RS-L: In my department, we perform all our molecular assays locally,



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because it benefits everyone involved. Turnaround times are shorter, there's no need to send out precious samples, and clinicians can directly discuss test results with pathologists. The pathologists get to work with advanced technologies and fully develop their professional skills. All parties appreciate the high-level pathology reports with clinicopathologic correlation.

MV: Our system is driven by clinical and patient needs and follows a basic rule: all tests that can be performed locally should be. If we encounter any problems with testing, a nearby university hospital can help us, but we try to carry out all routine tests in-house so that we build the expertise to handle not only simple, but also more complex cases.

What are the pros and cons of a centralized test model versus locally conducted testing?

PB: Centralized testing makes sense, for example, with a homogenous liquid biopsy or for certain biomarkers that are too rare to implement cost-effectively in every local laboratory. Unfortunately, some samples are sent out to hub laboratories – who potentially have lengthy turnaround times and could lack the pre-analytical assessment capabilities that some cases need – just to get the basic standard-of-care biomarkers. This is a waste of resources. We must focus on doing those routine tests quickly, cost-effectively, and as locally as possible.

FL-R: With the advent of NGS panels, genomic profiling has become more leaner, cheaper, and more user-friendly. Everything is quicker in-house, with much less chance of losing important material or information. One of the best arguments for in-house genomic profiling is the control it affords over the preanalytical parameters, tissue specimen selection, and sample quantity.

MV: I also see an ethical issue with sending samples to commercial laboratories abroad. In Germany, the healthcare system is over 90 percent publicly financed and, if you spend this money outside the system in which it was generated, you aren't supporting it and enabling its development – and this is an ethical problem.

Do you see value in increasing local knowledge and expertise in molecular testing?

RS-L: Yes. Pathology is one of the fastest-developing fields in medicine and molecular pathology is one of the fastest-developing areas in pathology. Soon, molecular pathology will likely be routine for confirming the diagnosis and prognosis of most tumors. Pathology departments not using these techniques will be left behind, so pathologists must develop expertise with the new testing methods – and with molecular pathology in general.

Have you experienced a move toward test centralization in your country?

RS-L: My hospital is part of a chain of institutions, and a few years ago, the decision was made to centralize our molecular pathology. The new central laboratory was not equipped to handle our testing needs, nor was it connected to our pathology department. Clinicians were not happy with the results or the fact that they could not properly discuss tests with the pathologists who had performed them. Eventually, the complaints mounted and the centralization attempt failed.

While this effort was underway, a wide gap developed between my hospital chain's capabilities and those of hospitals whose labs had not been centralized and it took us some time to catch up.

How can in-house testing benefit your interaction with your colleagues – for example, in multidisciplinary teams coordinating oncology patient care?

FL-R: When we started NGS, we set up an internal “intra-laboratory molecular tumor board” to discuss test results before reports are released and clinicians and patients apprised of the results. It's a formal meeting among the molecular



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biologists, pathologists, and technicians; we integrate the pathology information and individual biomarker testing with the NGS results and make sense out of the huge amount of information. This facilitates efficient conversation with not only our clinical colleagues, but also our patients, enabling them to understand and get the best value from their test results. It worries me that some people treat NGS results like something simple and straightforward, and think it's enough to just send results to clinicians. These are complex tests with a lot of information that must be interpreted and put into context for every patient's clinical situation and pathology context.

Reducing turnaround time (TAT) to result is a hallmark of in-house testing. How important is it?

PB: No clinician ever complained about high-quality results arriving too quickly for any test, oncological or otherwise. It clearly impacts patient care. But it is also important to understand that the speed at which your lab can operate is not the only factor influencing TAT. Under General Data Protection Regulations, if you deal with cross-institutional or cross-IT systems, you are likely to encounter test result delays. The same applies to transporting samples.

What's the value of keeping samples at your institution?

PB: This is the ideal scenario, and one of the problems with planned centralization is that people do not want to send out tissue blocks. However, if you outsource sections, curls, or slides from those blocks, you may be wasting material and not meeting preanalytical or sample requirement needs. Kept in-house, we can ensure that testers take only what they need from each sample.

RS-L: It is important to preserve as much as possible of precious patient samples. If you do your testing in-house, you can decide on the test flexibly based on amount of sample available. The centralized labs perform the same large over 500 gene panels on all samples and sometimes do not get any result as there just was not enough of the tumor material. This means possibly re-biopsy for patients and further delays.

Can any pathology laboratory today do genomic profiling for key predictive markers?

PB: From a technological point of view, I think we are near. The latest developments in PCR and NGS equipment are very much "sample in, result out." However, it will differ by country depending on the healthcare model. In the UK, following the 100,000 Genomes Project, there is substantial movement toward a few centralized molecular pathology laboratories. Some laboratories like ours, with existing skills and high sample volumes, are trying hard to "stay in the game" – but existing public sector pathology laboratories without molecular capabilities would probably struggle to establish them now.

FL-R: I agree. From a technical perspective, I can imagine that molecular profiling by efficient, actionable NGS panels will be relatively easy for most laboratories within a few years. But it all depends on how health systems organize their workflows. Currently, in Spain, most institutions have their own budgets and make their own decisions, but it's a very mixed picture.

RS-L: In Israel, currently most, even small labs can do molecular tests with simpler methods such as PCR, FISH, or NGS assays. Larger academic hospitals perform NGS. I think in future, NGS will likely become even more routine and will be done even in smaller hospitals, because it makes sense for the clinicians and their patients as well as for pathology labs.

MV: With the recent advances in techniques and technologies, most pathology labs can certainly do NGS. It has to be cost-effective, of course, and you need qualified personnel – although not necessarily bioinformaticians these days.

Do you have a take-home message to share?

FL-R: I'd like to advocate for seeing things from the patient's perspective. When we offer patients an NGS test, we also offer to discuss it with them. That tends to reassure them, because they value our honesty about the pros and cons of different treatment options, expectations, and possible problems. Ultimately, we need a patient-centered system, and that can only be achieved if we keep molecular profiling in-house.



PATHOLOGISTS: IN-HOUSE EXPERTS

The in-house laboratory is a valuable resource for both clinicians and patients

An interview with Ruthy Shaco-Levy

Could you describe how pathology fits into precision oncology?

Pathology is developing at light speed compared with other fields of medicine – and one of the fastest-developing areas is precision medicine. I think every pathologist deals with “precision pathology” – it’s an integral part of the pathology report. For example, if we find a case of breast cancer, we report on tumor grade, tumor size, and receptor status. Separating molecular pathology is artificial; why would you select one part of the examination process and complete it in a separate place?

Why do you test in-house at your institution?

Israel has a “national health basket” of drugs and diagnostic tests. Hospital laboratories perform all tests included in the basket. Initially, we did a lot of immunohistochemistry and PCR; now, we do much more of our testing with next-generation sequencing (NGS) because it’s more efficient and more accurate. It’s important for me as a pathologist to correlate my findings with each test result. For example, if I have a breast cancer case



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that looks like a low-grade lobular or ductal carcinoma and HER2 comes back strongly positive, I have to ask myself some important questions: Do the results make sense? Is my diagnosis correct? Ultimately, I might choose to repeat the tests or to confirm my diagnosis – and that’s something that can only really be done if you test in-house.

Also, we must not forget to develop our pathologists. Molecular pathology is an increasingly vital part of our profession and, if pathologists and laboratory medicine professionals aren’t given the opportunity to practice, we won’t be able to use those tools when we need them. We play a key role in patient care, and we owe it to them to keep our abilities honed.

Have you had experience with centralized testing?

A few years ago, my hospital chain tried to centralize our laboratory testing. Unfortunately, the lab was not equipped to handle our testing needs or connected to a pathology department and, to make a long story short, it failed. Over the few years of our centralization, a wide gap developed between our capabilities and those of hospitals that had not been centralized. Fortunately, since our testing moved back in-house, we’ve closed that gap.

Last year, there was an initiative to move all non-small cell lung cancer (NSCLC) NGS testing in Israel to a large commercial laboratory from overseas. The Israeli Association of Pathologists and other experts, including oncologists, strongly opposed this for many reasons: long turnaround times, loss of the ability to coordinate the patient care in cross-disciplinary tumor boards on-site, and more. As a result of this opposition, from July 2020 onward, local pathology departments will perform all DNA/RNA NGS analysis for NSCLC patient samples – the best possible outcome for patients, pathologists, and the healthcare system as a whole.

So what are the key benefits of in-house testing?

First, reducing turnaround time to results; some cancer patients have a very rapid clinical course and need test results right away – especially for companion diagnostics. If we send material abroad, it can take weeks to get the results. Patients can’t wait that long to start treatment, so they may receive ineffective or even harmful chemotherapy. Turnaround time is critical in pathology in general, and especially in molecular pathology for cancer patients.

Second, preserving precious sample. Many hospitals use smaller panels for their precision testing. In lung cancer, for instance, you can assay a few dozen genes or you can assay hundreds. The more genes you test, the more biopsy tissue you need – and the less remains for future tests. When we test in-house, we carefully select our tests based on the available material. By only asking the most important questions, we make sure there’s enough material to get answers.

And third, keeping tissue in-house. As noted, biopsy material is precious; sending it out risks loss or damage. Even if the sample reaches its destination safely, we may not receive any material back because other labs may test less conservatively, forcing patients to undergo another biopsy if they need further testing. It’s far safer to avoid sending tissue out at all.

It’s the pathologist – the expert – who selects the appropriate assay based not only on how much tissue is available, but also its quality. In-house, that decision can be made on a case-by-case basis, but central labs often apply the same large panels to all material – and those panels are “all-or-nothing,” so if there isn’t enough material, you can’t prioritize the most important genes. That means patients with insufficient high-quality tissue must undergo a repeat biopsy or risk having no answers at all – an unacceptable outcome that makes in-house testing vital for true precision oncology.

Ruthy Shaco-Levy is Professor and Head of Pathology at Soroka Medical Center, Clalit Health Services, and Head of the Israeli Pathologists Association, Beer-Sheva, Israel.



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ONCOLOGY BIOMARKER TESTING IS BEST IN-HOUSE

In-house testing enables direct communication between labs and treating clinicians and ensures local healthcare quality

An interview with Michael Vieth

How – and why – do you conduct precision oncology testing at your institution?

When a clinician asks us to perform a specific test, our first step is always to identify the most suitable methods. By carrying out all testing in-house, we can adjust these methods to best suit each individual sample, maintaining regular communication with our clinicians to align testing with clinical needs. This benefits the patient because we can provide an immediate response to the treating oncologist, asking for further samples or information if necessary.

In centralized testing, specimens are sent to an external laboratory, which carries risks – for instance, logistical problems with the transit of material or communication issues because there is no direct contact with a physician. By avoiding these issues, in-house testing saves time and money. The entire diagnostic process comes from one source and we aren't left waiting for an organization to provide analyses without medical advice.

It's the rare and complex cases that really benefit from in-house testing, because those who conducted the analysis are available to discuss the results. However, different labs have different needs; to



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ensure that in-house testing is a sustainable option, there must be enough tests required to make the investment worthwhile.

How do different regional costs affect the choice between in-house and centralized testing?

The price that central labs charge for testing varies between regions and countries. Some labs send specimens abroad to be tested – but passing public money from one health system to another raises ethical concerns. Even if specimens are sent to central labs in the same country, they could be outside the national health system and therefore benefit external stakeholders. Different regional costs can also lead to legal issues. Regulations and side costs vary between countries – and if samples sent elsewhere are cheaper to run, that advantage must make its way back to the patient or healthcare system. If the more expensive local price is paid, then the difference could end up as profit for the central lab, which is illegal.

How does test centralization impact local healthcare?

Driving more testing through central facilities can lead to local laboratories “drying out” as knowledge, tests, patients, and money get drawn into the larger central facilities. The biggest damage that I see from losing routine cases is that you lose the ability to carry out basic science and research, which is crucial for many local facilities. Without a certain number of cases on which to demonstrate a particular testing method, it is impossible to educate people. Routine cases are an important part of the educational services of local institutions that offer medical courses – and, for complex tests that require detailed background knowledge, there’s no way to learn if cases (and pathologists experienced in diagnosing them) are not available.

It’s also easier to maintain tissue blocks if they are kept in-house. We have a strict tumor bank and receive up to 10 requests per day from external researchers for samples – but we always request that they

return the samples without stepping down the blocks completely.

How does in-house testing make it easier to coordinate patient care?

We recently received a call from the intensive care unit. The head anesthetist had sent me a sample of bronchoalveolar lavage and told me that they suspected the patient had vaped something with an e-cigarette, so we should look for macrophages and lipid-loaded cells. We were able to react to the situation immediately in a way that would not have been possible had the sample been sent elsewhere, because it’s often difficult to reach people at central labs by phone. A pathologist’s second most important tool – after the microscope – is the phone, which is frequently used to retrieve information missing from cases. I often find that, especially in centrally managed labs, people fail to provide all of the necessary details about a certain case. This can be frustrating and delay diagnosis or treatment, so moving testing in-house means that you can collaborate easily and follow up quickly if any information is missing.

Another benefit comes in the form of turnaround times. Our clinicians often call at midday on a Friday and request an urgent test – for example, to determine whether a patient has a particular virus and shouldn’t be allowed home over the weekend, or whether or not a patient should start immediate chemotherapy. We can usually provide an answer that same day, which wouldn’t be possible if we sent the sample to a central lab via an expensive courier that might not deliver the specimen before the following week. If everything is sent externally, the in-house lab will eventually lose the expertise to carry out these urgent cases. Even if 90 percent of cases are routine, it’s these few urgent ones that really prove the value of in-house testing.

Michael Vieth is Professor of Pathology and Chairman of the Institute of Pathology, Klinikum Bayreuth, Germany.



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PRECISION ONCOLOGY FLOURISHES IN-HOUSE

The UK is headed toward test centralization – but the value of in-house testing must not be underestimated

An interview with Tanya Ahmad

The UK's 100,000 Genomes Project reached its goal of sequencing 100,000 entire patient genomes in December 2018. Capitalizing on this success, January 2019 saw the establishment of a new, nationally commissioned Genomic Medicine Service that harnesses seven Genomic Laboratory Hubs around the country. The goal is to standardize the criteria for whole genome sequencing and targeted panel tests, simplifying patient pathways and reducing social inequalities – but is this democratization of genetic testing the best option for all institutions? We spoke to Tanya Ahmad, Consultant Medical Oncologist in London, to discover her personal outlook on in-house testing versus centralization.

What is your background in medical oncology?

I've been practicing as a lung cancer consultant for over nine years, a role that began just as precision medicine was beginning to flourish. I currently work across two institutions, which puts me in the interesting position of seeing things from two different perspectives. At one of my institutions, all testing is currently conducted in-house. All samples from the diagnostic teams (lab) – from CT-guided lung biopsies to EBUS/bronchoscopies – are sent to the histology lab



on our campus. Once we've established a diagnosis of lung cancer, the sample is subject to immunohistochemistry tests and, following that, the curls of the tissue block are sent to our affiliated molecular pathology lab. Although these three steps are all carried out within one institution – i.e., “in house” with all the benefits – it is a relatively large campus and we have observed that even small changes, for example, to the location of the pathology labs, can potentially impact the delivery speed of test results.

The pathology pathway at my other institution is more complex because three geographically distinct hospital sites have merged.



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Biopsies performed in one location must often be transported to another for basic H&E/IHC examination – and then molecular testing is further outsourced to another central lab. Experiencing the two contrasting strategies in parallel is like having my own controlled experiment in which I can directly compare in-house and somewhat centralized testing.

Why do your institutions approach things differently?

It's a combination of historical pathways, institutional politics, and the availability and quality of local support services. At the institution that conducts in-house testing, we've practiced molecular pathology for many years and we were routinely carrying out next-generation sequencing (NGS) before most other trusts. We also have a strong academic and research focus, so testing was already part of our standard pathway. In contrast, at my other institution, two district general hospitals merged with a larger teaching hospital. This meant that many services and departments were drastically reconfigured over the course of two years. We transformed from a place that conducted all testing in-house (before the advent of routine molecular testing for cancers), first to sending samples to another city and then back to sending them to other centers in London. Trust mergers often involve the reconfiguration of many services and pathways, a process dictated by the consolidation of expertise and various other cost implications of centralizing services.

Having seen both sides of the story, what's your opinion on test centralization versus regionally conducted testing?

There is a lot of heterogeneity in terms of cancer services, care pathways, and patient outcomes across the UK, part of which might be related to rapid diagnostics and patient access to clinical trials and certain drugs. The attraction of centralization is that some peripheral hospitals without adequate resources or academic expertise can access NGS, providing more detailed information about a patient's tumor than otherwise possible. Having access to a central hub that facilitates this can improve patient care – even in the face of increased turnaround times. However, in a center that already has the facilities

and expertise to carry out NGS testing and other more sophisticated genomics, centralization is unlikely to add any benefit. If you already have a system that works in-house, centralization can introduce pitfalls, such as complex lab standard operational procedures, longer turnaround times, or increased risk of losing samples in transit.

From my point of view as a medical oncologist, one of the main benefits of in-house testing is the personalized service. I know the individual multidisciplinary team (MDT) colleagues dealing with samples because I meet and talk to them every week and, if an issue arises, I can contact them directly and informally to discuss the problem. Good MDTs improve integration between pathologists, radiologists, and oncologists, all of whom might previously have worked in separate silos. There's an interest in each other's specialties and, as a result, a deeper understanding of the nuances with individual cases. For example, I can call my colleagues about a particular patient and explain that, although we would usually request NGS testing for EGFR, this is a very young individual who is extremely unwell. Their demographic raises strong suspicion of an EGFR mutation so, instead of waiting two weeks for the NGS results, we'd like to request a rapid EGFR test with a 48-hour turnaround time so that we can begin treatment faster. With centralized testing, each sample is anonymous – just tumor material with a serial number, perhaps lacking detailed clinical information that might help with analysis. It's harder to have the same nuanced conversation with a central laboratory, because you don't know the person you're speaking to and they may not be as invested in the case as your in-house pathology colleagues. In my opinion, this is another aspect of "personalized" care.

General interaction with colleagues is another benefit; delayed results can still occur in house – but, unlike with centralization, you can easily pick up the phone and speak to the pathologist. They can then check where the sample is in the pathway and call back within minutes to confirm when the results will be available. When I've sent samples externally, there is a phone number to call, but the person on the other end often can't provide much of an update and I'm left waiting for a response. The process becomes much longer and more challenging, which is why in-house testing can be beneficial for institutions whose internal labs possess all the clinical information



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and technical facilities to fully trust their results. It's also important to maintain laboratory skills and academic expertise within the institution; molecular pathology is a fairly niche subject, especially as more actionable, but rare molecular targets are identified. Therefore, centralization of molecular analysis may compromise the training and experience of newer generations of pathology colleagues who won't be exposed to it without internal facilities.

What are the consequences of an extended turnaround time for patients?

Delays are potentially clinically harmful – especially for lung cancer patients, who often present in the advanced stages of disease and with comorbidities that affect their suitability for treatment. An inadequate test result or a lost sample could be the difference between starting treatment within days or within weeks – and, because patients need to be relatively fit for certain therapies, rapid deterioration can mean they miss the opportunity for treatment entirely.

Long turnaround times are also frustrating for the patient. After being diagnosed with lung cancer, it's often possible for them to see the oncologist on the day they receive the news – but my scope for discussing any systemic treatment with them is limited until I have all the molecular test results. Even with optimally functioning in-house testing, this can take up to two weeks (during which the patient must sit at home, knowing their diagnosis, but anxiously awaiting next steps in management). That's extremely difficult even without delays, so any extension in turnaround time as a result of centralized testing can have a significant negative impact on patient experience and outcome.

Are there any other potential risks of test centralization?

There have been occasions when samples were lost due to the convoluted nature of centralization. There are more opportunities for errors because there are several steps in the process that are out of my institution's control. Every step is someone else's responsibility

– and when we tried to identify issues using pathway mapping for our pathology services, it merely revealed how complex each step was. One solution we derived from this mapping was to coordinate the specimen bags by color to highlight the most urgent samples for couriers. This minor change made a noticeable improvement to turnaround times, emphasizing how much variation there can be at each stage of the process.

Another concern is ownership. Who takes responsibility for the samples once they leave the trust? If the courier gets lost or the samples are misplaced, do you wait for someone to search for them while the patient deteriorates? Or do you return to the patient, apologize, and obtain another biopsy? The latter might ensure faster results, but biopsies can be unpleasant, taxing, and sometimes inconvenient experiences – plus, there's always an element of risk. Why should the patient have to undergo another procedure because there's a flaw in our pathway?

From an academic perspective, I completely understand how central testing benefits certain services. However, I don't think those advantages apply equally to all hospital trusts – and I'm not convinced that implementing “blanket” centralization was necessarily the best move in the UK, especially when we are striving to reduce cancer treatment waiting times. We've already found that molecular test centralization can be time-consuming with respect to both admin and turnaround times. Whether this problem improves or worsens as throughput at central lab hubs increases remains to be seen. It's clear that institutions without an effective testing service of their own can certainly benefit from test centralization – but, for others, supporting and maintaining effective and efficient in-house testing remains the best way to optimize patient care.

Tanya Ahmad is a Consultant Medical Oncologist in London, UK.

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LEARNING AND GROWING WITH IN-HOUSE TESTING

Keeping molecular testing in-house offers benefits for pathologists, oncologists, and patients

An interview with Wei Song

How – and why – does your institution conduct precision oncology testing?

Precision medicine is a newly evolving discipline and, to fully realize its potential, all adequately sized institutes should be able to provide in-house genomic profiling for tumors from both tissue and plasma samples. I always think as though I'm running a startup company, so my number one consideration is the customer – who are they and what do they need? Our customers are oncologists and they need genomic profiling tests to enable their patients to benefit from novel precision oncology treatments.

Also, I believe molecular diagnostics is the future of pathology. So while centralization plays an important role currently, if we don't practice in-house testing, we won't be able to develop alongside the science and provide the best possible standard of care. That's why we do as much as possible in-house – to support our clinicians and patients and to keep learning and developing.

Have you participated in a move toward test centralization?

The opposite, in fact. In our institution, all testing was initially sent to a



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central laboratory – but, ever since we established molecular profiling in our lab, it has come to us instead. Bringing our testing in-house was a real game-changer for the oncologists, for the institution, and for the entire community.

What do you think about test centralization and its promotion by large commercial laboratories?

First, it's important to look at the central laboratories' testing success rates. Some of them are unable to test as much as 30 percent of patient samples due to limited size and tumor content. Because we can test even very small samples in-house, our success rate is 98 percent. The second thing to consider is turnaround time. We provide results in three to four days. Most of the central labs can't compete with that; it takes them one to two weeks – a huge difference. Third, pathologists and oncologists must work together to examine each patient case individually. Sometimes, we need to drill down to the detailed results and assess everything in clinical context. It can be extremely difficult to get detailed data from a commercial lab – and it might take up to a month. In-house, we're ready 24/7. Any time a clinician calls us, we can jump on the computer and review the data with them virtually. This is hugely important for them – and it's no less important for our development and for the research that drives modern medicine.

Precision medicine is in its infancy, so continual development is key and every case deserves a thorough investigation. If you look at the molecular testing report without also having the opportunity to examine the raw data and interpret the results in context, you won't be providing the best possible service – and you'll be depriving yourself of the chance to learn and progress.

How does in-house testing contribute to better patient care?

First, we facilitate and improve patient care by providing results much faster – and for many more patients – than a central lab. We also participate in tumor boards and, as I mentioned, we have regular

telephone conversations with clinicians. This level of interaction is not possible when sending out tests to a central lab. I have had experience communicating with central labs; usually, the people I spoke to were not trained pathologists and lacked the expertise to address my questions.

The difference in turnaround times is also hugely important. We are talking about patients for whom even a single day – let alone a week or two – can make a lifetime of difference. Often, oncologists ask for urgent results because their patients are deteriorating. Cancer doesn't take weekends off. Whereas a central lab might take two weeks to provide those crucial results, we can be flexible and expedite delivery.

There's also the question of potential sample loss. Sending FFPE tissue blocks to a central laboratory means taking on the risk of losing them. That can lead to tragedy because, often, one result is not enough; we want to confirm that result via another method. If we don't have the block, we can't do that – and, in the future, we can't use those samples for further testing or for clinical research (another way in which we support our oncologist colleagues). That's a loss for the patient, the pathology department, and the institution.

What would you most like to emphasize?

The number of targeted therapies is growing and, one day, the standard of care will include a genomic profile for every tumor sample to help to guide treatment decisions. If we want to train the next generation of pathologists to understand molecular pathology and cope with these novel demands, they must be exposed to the entire testing process to give them the necessary education and experience.

Wei Song is Director of the Clinical Genomic Laboratory at the Englander Institute for Precision Medicine, Assistant Professor of Pathology and Laboratory Medicine at Weill Cornell Medical College, and Assistant Attending Pathologist at the New York-Presbyterian Hospital, New York, USA.



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PRECISION ONCOLOGY'S GREATEST TOOL?

The power of in-house genomic profiling is felt by both patient and pathologist

An interview with Rui Manuel Reis

Tell us about your background in oncology...

I've worked in cancer genetics since 1996. I started out studying microsatellite instability, then moved to molecular pathology for my PhD. In 2010, I moved to Barretos Cancer Hospital, where I coordinated the implementation of the molecular diagnostics laboratory. It's one of the largest cancer hospitals in Brazil and, because we only attend to the Brazilian public health system, treatment is free of charge. We do something that is unique in Brazil – deliver state-of-the-art diagnostics and treatment to people who cannot afford private healthcare. And is something we are incredibly proud of.

What are the benefits of precision oncology – and how does genomic profiling play a role?

Put simply, precision oncology allows us to determine the best approach for each individual cancer patient. Genomic profiling is a crucial tool to guide treatment decisions and select a drug that targets each tumor's particular molecular profile. We mainly use



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next-generation sequencing because we can evaluate both DNA and RNA alterations, such as gene mutations and fusions. We plan to increase the number of genes reported by tumor type and evolve into a liquid biopsy approach, as well as expand into the use of gene expression signatures.

What is your opinion on in-house testing versus centralization?

We perform in-house testing as it allows us to control the whole workflow – from tissue selection and sample manipulation to generating reports for our clinicians – and we believe that ensures our patients receive a higher standard of care.

In Brazil, most tests are expensive – particularly in centralized labs. But when we test in-house, we can choose the best, most cost-effective method for our needs, giving all patients access to the information that will guide treatment decisions.

Also, it is important to preserve the sample material because it might be required for future tests. Because we have complete control over the tissue block, we can use only what is necessary for our chosen assay. Many centralized labs don't take the same approach – they use large panels to avoid repetition and often exhaust the sample.

In-house testing also avoids the delays that centralized labs face – the turnaround time is much shorter. This difference is even greater in countries like Brazil, where couriers have to travel long distances.

Finally, because we are a teaching hospital, we can also provide a better training foundation for our interns; not only do our current patients benefit from in-house testing, but our future patients will as well.

How does in-house testing help you address Brazil's new general data protection regulations?

Genetic data is now categorized as sensitive data. If you want to perform a test, you must obtain written consent from the patient – but we already do that when they are admitted. Sending samples abroad to centralized labs adds a layer of complexity because the patient needs to sign another form specific to the lab receiving their samples. Again, having the in-house lab accelerates this process and provides a faster result for the patient.

How does it affect your collaboration with clinicians?

In-house testing allows us to have conversations about the results with our clinicians during multidisciplinary tumor boards. This helps them better understand the findings, ask questions, and plan the best treatment for each patient, which ultimately leads to better care and outcomes.

What are your thoughts on pharmaceutical companies' paying for samples to be tested in centralized labs?

I think the problem lies in the size of the panels these labs use. Although broad-spectrum diagnostics may be a great tool in future, there are still only a few drugs available to us that have clear benefits for patients. In my opinion, it's not ethical to perform a test that generates results that are not actionable; that only gives patients false hope. That's why, at my hospital, we only perform tests that guide real treatment options.

Rui Manuel Reis is Coordinator of the Molecular Oncology Research Center, Barretos Cancer Hospital, Barretos, São Paulo, Brazil.



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IN-HOUSE TESTING AND THE PATHOLOGIST- ONCOLOGIST RELATIONSHIP

Keeping tests close to home allows the lab and the clinic to work closely together

An interview with Alain Mita



Tell us about your background in precision oncology...

I am a medical oncologist who treats mainly lung, head, neck, and thyroid cancers. For lung and thyroid cancers, molecular tumor profiling is becoming increasingly important. In fact, at this point, there's no way you can treat a lung cancer patient without a molecular profile – and you need it as early as possible to help make treatment decisions.

I'm also Co-Director of the Experimental Therapeutics Program. Many new drugs in the pipeline are molecularly targeted based on genetic and molecular findings in tumors and blood. And, finally, I also co-chair our molecular tumor board, in which we discuss prospective cases with molecular pathologists and other specialists to help us determine the right treatment approach for patients with complex genetic findings. So I clearly have a vested interest in precision oncology from many angles!



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How is precision oncology conducted at your institution – and what inspired that approach?

For many years, medical oncologists have understood that we're moving away from purely histology-based treatment toward molecular-based treatment. In other words, the tissue or organ origin of the cancer is no longer as relevant as its molecular profile. We have seen that different types of cancer can share the same driver mutations – for instance, BRAF mutations are found not only in melanoma, but also in lung and thyroid cancer. We know that a tumor's molecular profile and driver mutations are critical, so we think that treating patients based on these data is the way to go. We try to characterize as many of our patients from a molecular standpoint as possible and make treatment decisions based on the results.

We also have a molecular tumor board at Cedars-Sinai because not all medical oncologists are familiar with cancer genetics – and some cases are complicated even for those who are. The molecular tumor board is the perfect venue to discuss complex cases and make treatment decisions.

Finally, we're conducting an investigative trial here in which we prospectively analyze the outcomes of patients who are treated based on their molecular profiles versus those who are treated without that information. Similar studies have been conducted retrospectively – ours, which should yield results in about a year, is the first to take a prospective view.

What's your opinion on in-house versus centralized testing?

For many years, our molecular testing was exclusively in-house. Now, we have both in-house and outsourced testing – a mixed model.

I think there are pros and cons to each method. For in-house testing, the pros are shorter turnaround times and the availability of local molecular pathologists to discuss

complex cases with oncologists and drive a more personalized approach. The disadvantage is that it's more expensive; the technology evolves very quickly and you have to make sure that your institution stays up-to-date. When we began, we used a 50-gene panel – but, soon after we implemented it, we moved to a 150-gene panel. Now, we even use a 500-gene panel in some cases! It's not always easy for institutions to keep up and the cost can be prohibitive.

Centralized laboratories who do this kind of testing in bulk have more freedom to continually update their technologies and databases. The disadvantages are numerous, though. You have to send your tissue out, which creates problems – did you send out the right tissue? the right amount? high enough quality to yield reliable results? The timelines also present a challenge; it takes about two weeks to get a result back from a central laboratory, whereas in-house testing can return results within days. And it lacks a personal touch; you get the reports, but not the direct contact with your laboratory colleagues.

So what are the biggest benefits of in-house genetic profiling?

Turnaround time is one of the big advantages. I recently had an elderly patient with lung cancer who was not a candidate for chemotherapy, so we needed to decide between immunotherapy and targeted therapy. We didn't want to make the wrong decision, because the sequence of treatment matters; the risk of side effects from targeted therapy is much higher after immunotherapy. The decision had to be made quickly, so we did an in-house panel and chose a treatment right away. I don't know what would have happened if we had waited three weeks for results from a central lab.

Sometimes, samples are even lost in transit – and, when that happens, the consequences for patients are very serious. Because the information is so vital, we usually repeat the



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biopsy if the original sample is lost. That is neither pleasant for patients nor devoid of risks, so the less often we send samples to central laboratories, the better.

I also think in-house testing is better for tissue preservation. Pathologists know exactly what they can do with a given amount of tissue and how much sample is needed for each test. In-house, we can perform bespoke testing, rather than simply sending the tissue to a central lab for pre-selected genetic tests. The molecular pathologists also help us decide between (or combine) treatments when tests reveal multiple actionable targets.

Should everyone be testing with large panels – is bigger always better?

This is a tough question. Doctors need quick answers, which is why sequential testing isn't a good option. In an ideal world, the more genes you test, the better. The problem is that, when you test a large number of genes, most are not relevant or actionable. It can be valuable to know that a patient has a specific mutation – but, if there isn't a treatment to target it, the additional knowledge doesn't translate directly into better treatments or outcomes.

Sometimes, having a huge amount of information that you can't really apply becomes counterproductive – and that's where the balance becomes difficult. I don't think there's one right answer, but "bigger" is not necessarily "better." Information

curation is a critical part of testing, too. Whether you have a little information or a lot, the key lies in asking the right questions – and that's where teamwork between molecular pathologists and oncologists can help, especially if the testing is conducted in-house.

How do you work with your colleagues in pathology?

At our institution, molecular data is an integral part of the electronic medical record (unlike results received from central labs). That helps us not only with patient care, but also with clinical research – if we can link the tests to treatments and outcomes, we can learn more about how (and why) our treatments work.

We also have strong communication between pathologists and clinicians – personalized according to our preferences. Some receive phone calls, some emails, and some, like me, prefer texts. That way, we get results conveniently and in real time, allowing us to act fast. Our relationship with our colleagues in the laboratory is invaluable; in-house testing allows us to develop it to the best possible advantage – for us and for our patients.

Alain Mita is a medical oncologist and Co-Director of the Experimental Therapeutics Program at the Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai, Los Angeles, California, USA.



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BIOMARKER TESTS FOR PRECISION ONCOLOGY: DIY OR PAY-FOR-SERVICE?

An expert panel discussion

When testing for cancer biomarkers, hospitals and healthcare systems must choose between developing in-house capabilities or purchasing outsourced services. But what's best for the system – and what's best for patients? To discuss this, we convened a panel of oncologists and pathologists with broad expertise in precision oncology biomarkers: Carl Morrison (Roswell Park Comprehensive Cancer Center, Buffalo, New York); Kojo Elenitoba-Johnson (Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania); Alain Mita (Samuel Oschin Cancer Center, Cedars Sinai, Los Angeles, California); and Wei Song (Englander Institute for Precision Medicine, Weill Cornell Medicine, New York, New York). Moderated by Michael Schubert (Editor of The Pathologist) the panel explored the current state of biomarker testing – and the merits of keeping such testing in-house.

How does your institute organize precision oncology tests?

Carl Morrison: At Roswell Park, we perform mosts tests for our own patients; some are for outside parties, mainly local doctors.

Kojo Elenitoba-Johnson: At the University of Pennsylvania Health System, we also focus mainly on our own patients. We opt for in-house testing wherever possible; that said, some tests must be outsourced.

Alain Mita: At Cedars Sinai, we use both in-house and outsourced testing.

Wei Song: At Weill Cornell, in-house is the default.

What are your thoughts on centralized versus in-house testing?

WS: I believe that in-house molecular diagnostics capability is indispensable – no pathology practice is complete without it. Furthermore, in-house expertise is vital for educating future residents. Finally, in-house facilities better meet oncologists' needs regarding type and size of assay panel – and, in particular,



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turnaround time. Our clinicians' top priority is rapid assay of 20–30 variants for immediate input into clinical management. Speed is key!

CM: Agreed; up to 98 percent of clinical decisions are based on a small subset of biomarkers. Doctors want fast results for that subset, not slowly delivered data for every single marker of potential interest. It's true that in-house laboratories may not be able to duplicate the infrastructure found in a commercial institution performing thousands of tests annually – but, when turnaround time is key, in-house is better. Remember, it can be time-consuming to transfer clinical samples, such as bone marrow biopsies, from hospitals to central laboratories.

AM: Yes – the logistics of sample transfer is a critical point, because doctors need assay data as early as possible in the clinical management process. In lung cancer, for example, the best outcomes require mutation-specific therapy. And initial therapy choices may have big impacts – immunotherapy followed by mutation-targeted therapy gives more severe side effects than the converse. Rapid decision-making also helps patients psychologically. After diagnosis, they want to start treatment as fast as possible, so turnaround time is of the utmost importance. Another advantage of in-house testing is that physicians can access their molecular pathology departments for expert advice. Because assay interpretation can be difficult, even for those familiar with molecular testing, this is an important advantage that centralized laboratories cannot offer.

KEJ: Three parameters influence the in-house versus outsourcing decision. First, the nature of the institute's patients; why invest in a test if its patients don't need that test? Second, infrastructure and capital expenditure considerations; building next-generation (NGS) capability requires hardware, software, trained personnel, and regulator-acceptable systems. Finally,

bottom-line factors such as reimbursement also influence an institution's precision diagnostics strategy. In some cases, outsourcing may alleviate patients' cost burden. In others, patient volumes may affect the bottom line; if few patients need a given test, offering it may not be cost-effective. That said, there are often trade-offs between the cost advantages of outsourcing and its slower turnaround time.

WS: Another point: in-house facilities help oncologists to better serve patients. For example, if we have insufficient material for the assay – which does happen – we can simply ask for more.

Can in-house testing promote team-based coordination of patient care?

AM: Yes. A key advantage of in-house testing is collaborative decision-making. As a clinician, I place a high value on interactions with molecular pathologists. These range from phone calls and emails regarding urgent decisions to molecular tumor boards where we discuss complex cases that benefit from a variety of expertise.

WS: I agree. I regularly discuss data interpretation with my oncologist colleagues. For example, in complex cases – such as patients with two targetable molecular drivers – we employ methods to identify the dominant driver and design more effective care. It's all about patient benefit.

CM: The in-house environment also enables interactions with medical directors and payers. A phone call to discuss the situation can help to prevent a patient's treatment being denied. By contrast, centralized routes involve large, impersonalized systems; interaction is difficult and patients may be denied out-of-pocket costs.

KEJ: These discussions also benefit primary care providers, not just those at the tertiary center.



Are all tumor boards becoming molecular tumor boards?

KEJ: In our center, yes. And, in my experience, the molecular tumor board often extends across institutional boundaries. For example, the referring institution or academic institutions may be included, often via telemedicine systems. I believe the reach of the molecular tumor board will continue to grow. After all, there is a natural synergy between oncologists, pathologists, and genomicists.

WS: I'm not so positive about separate, dedicated molecular tumor boards – but I do like the idea of integrating genomic profiling into routine tumor boards. Outlining translation pathways and available targeted therapies is very helpful for oncologists.

AM: Identification of clinical trials that may address a patient's mutation profile is also extremely helpful; molecular tumor boards can provide this information as well. The only problem is that you can't have such meetings in real time; they can take a couple of weeks to set up. But, in the future, I anticipate that most discussions will be integrated into these tumor boards.

What should we aim for in terms of communication speed?

CM: Molecular pathology laboratories should get reports back to oncologists within six days – preferably three or four. Ideally, structured data should be uploaded into the electronic health record as it becomes available, even if the complete report is not ready. And the lab should answer queries very rapidly – certainly within 24 hours.

KEJ: I completely agree. We must deliver accurate, clinically relevant results on a timescale that is relevant to the patient's treatment. But turnaround speed depends on a large number of factors, many of which are somewhat institute-specific. The ability for clinicians to follow-up is also important.

How is precision oncology testing evolving?

CM: Molecular pathology in Roswell Park began about 15 years ago with single-gene tests and advanced to NGS in 2012. Our in-house panels became the basis of a spinout venture in 2015 – and now we are broadening our in-house capabilities again, including new NGS tests.

KEJ: We have gone from classical cytogenetics to NGS. For the last six years, all such tests have been performed in a single division comprising both scientists and clinicians with subspecialty certification from the American Board of Pathology and Molecular Genetic Pathology. The test volumes rise each year, as does the range of assays – it only takes one peer-reviewed publication to add to the list of genes relevant to precision oncology! At the same time, we vary the tests we perform according to the nature of the patients we treat and the turnaround times of the platforms we use. Accordingly, we remain dynamically reactive to the changing biomarker assay environment. More broadly, we expect that, in the near future, any pathology lab will be able to profile the key subset of predictive biomarkers. After all, WHO guidelines now recommend molecular testing to support diagnosis of many cancers. The future is molecular!



A PRECISION FUTURE FOR NGS TESTING

An interview with Garret Hampton

What is the Thermo Fisher Scientific Clinical Sequencing Division's role in precision oncology?

Thermo Fisher Scientific plays a key role in precision oncology. A decade ago, we introduced the Ion Torrent Next Generation Sequencing (NGS) technology as a research tool, and five years ago we launched our first OncoPrint assay for precision oncology research. Since then, we have enabled precision medicine for many laboratories around the world with a number of OncoPrint solutions across different applications, including immuno-oncology and genomic profiling from liquid biopsy. NGS technology's ability to test multiple cancer-associated mutations at the same time has been instrumental in building the case for its utility. Three years ago, we introduced the first US Food and Drug Administration (FDA)-approved NGS test, the OncoPrint Dx Target Test, for non-small cell lung cancer. It has since been used around the world to test patient tumors and identify mutations to be targeted with precision therapies. I believe we are at the heart of the precision revolution, working closely with researchers, pharmaceutical companies, and laboratories to make precision medicine a reality for patients.



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What do you personally believe in – centralization or in-house testing?

There are situations in which central testing makes sense; however, for personalized medicines to be more broadly used, testing must be done close to the patient. That's not only because of the critical time factor involved, but also to enable the multidisciplinary teams who manage the cancer patient to collaborate effectively.

You recently launched a new NGS system that can enable much broader implementation of in-house testing. Can you tell us about it?

I must clarify that the system is currently for research use only, although all of the consumables are manufactured at ISO 13485 certified facilities. However, we plan to take it through the regulatory processes in multiple countries.

The Ion Torrent Genexus system was developed to enable NGS democratization. It is the first turnkey NGS system, meaning that any technician – even with no previous NGS expertise – can easily operate it with minimum hands-on time. It can deliver the results in as little as 16 hours, enabling a broad spectrum of laboratories to use the technology and embrace NGS utility.

Can you be little more specific about the IVD plans?

We intend to register the instrument with both the FDA and the European Union in accordance with their Directive on in vitro diagnostic medical devices (IVDD). Soon after, we will also

register it through the 2017/746 regulation on in vitro diagnostics medical devices (IVDR). We are actively engaged with the regional regulatory agencies to obtain all necessary requirements and supporting documentation to finalize our plan.

You might have heard that the FDA has recently granted a breakthrough device designation to the future Oncomine Dx Precision Test for identification of low-grade glioma patients with IDH1 and IDH2 mutations who may be eligible for vorasidenib, an investigational treatment in phase III trials. This is one example of the many diagnostic claims we are working on in collaboration with pharma companies, developing CDx tests for targeted therapies in development. This is one of the key steps on the journey to making Genexus an IVD.

What else lies ahead for the Clinical Sequencing Division?

We strongly believe that NGS technology like ours will play a significant role in precision oncology testing now and in the future. Its simplicity, speed, and minimal tissue requirements are unique and important to the field. This has been one of our key focus areas and we anticipate building on that strategy moving forward. Although we will be focusing heavily on oncology, the Genexus system is also well-suited to other clinical testing areas. I believe that this overall strategy plays to our strengths – but, where we see benefit in other clinical segments, we will partner with other key players to ensure that Genexus is as broadly used as possible. We are very excited about the future!

Garret Hampton is President of the Clinical Sequencing Division, Thermo Fisher Scientific, San Diego, California, USA.

