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Analyse This

The ongoing drive for personalised medicine gives opportunities for pathology to broaden its reach beyond disease diagnosis and classification – but achieving this depends on central labs overcoming the challenges around sample analysis and doing readings on a global scale

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Demand for anatomic pathology services within clinical trials is on the rise, driven by shifting approaches in translational medicine and clinical development, together with a heightened need for more consistent and less variable tissue analysis and interpretation. The backdrop of this evolution is the continued emergence of personalised medicine, where advances in molecular diagnostics have led to discoveries in how individual genes interact – findings that are not only helping to predict disease, but also customise treatments and guide hopeful cures.

At the same time, these dynamics have contributed to an increased reliance on central laboratories to perform pathology testing for clinical studies. There is a growing understanding of the significant difficulties in correlating results between multiple pathology labs, as well as the benefits of applying the same techniques and standards to the meticulous process of embedding, cutting and staining samples throughout the trial. Pathology support from central labs can also aid sponsors in making more informed decisions on including or excluding particular patient populations – potentially avoiding the difficult scenario of having to amend a protocol.

Nevertheless, considerations around lab services in general is just one component of many in the clinical trial continuum, and can often get lost in the shuffle during study initiation and start-up. For pathology, specifically, there remain several limitations to effectively conducting these critical readings of treatment effect, and doing so on a global scale.

Identifying the critical skills necessary for pathology teams in this new climate is paramount, as is implementing the practical advances best suited to overcome the pathology challenges in trials – with the ultimate mission of guiding sponsors and sites toward a successful study.

Personalised Market

Impacting the field of pathology in recent years have been growing industry pursuits in personalised medicine – a market projected to total more than $30 billion by 2018 (1). Driving much of the activity is the increasing use of molecular biomarkers in clinical development and healthcare decision-making. Companion diagnostics, for instance, have become key determining factors for healthcare delivery. Overall, diagnostics reportedly influence up to 70% of all healthcare decisions (2,3).

The major expectations for personalised medicine are to both optimise therapeutic outcomes and reduce the frequency of adverse drug reactions, with the combined result providing a positive effect on health economics. Development and diagnostic companies are expected to benefit as well from lower discovery, development and commercialisation costs, and more specific market subtypes (4). Personalised medicine reportedly has the potential to reduce healthcare costs by $750 billion annually (3).

In oncology, biomarkers are associated with the majority of targeted and immunotherapies currently in development. Recent drug approvals for advanced melanoma and non-small cell lung cancer have also spotlighted pathology's role in detecting the genetic drivers of cancer.

In addition, patients with leukaemia or metastatic breast or brain cancers are now routinely offered a molecular diagnosis in many clinical centres, allowing physicians to select tailored treatments (5). Perhaps most notably, in breast cancer, testing platforms – including fluorescence *in situ* hybridisation and immunohistochemistry (IHC) – have been used to detect the human epidermal growth factor receptor 2 (HER2) mutation since 1998.

Therapeutic Reach

The focus on personalised medicine has opened up new opportunities for pathology to broaden its reach beyond primarily the diagnosis, classification and subclassification of disease. With the introduction of numerous ancillary tests over the last two decades, pathology is now not only identifying disease presence, but how the specific properties and hormone content of an individual's tumour, for instance, directly correspond to how that person will respond to a particular therapy.

While much of the buzz has been in oncology, these predictive technologies will likely take hold in many other therapeutic areas, including autoimmune disease and central nervous system disorders. These tests are likely to be developed at research and academic centres, but then ultimately expand out to larger community centres (6).

Disease Subspeciality

Amid the influx of these more targeted approaches in clinical development is a greater emphasis on the need for pathologists to be well-versed in disease subspecialities. For example, in the area of sarcoma, a rare form of cancer, a traditional pathologist may only review 10 to 15 cases a year; however, in a clinical trial that number will likely be in the hundreds or more, depending on patient enrolment.

Subspeciality experience is also critical due to the limited information afforded to trial pathologists, who are routinely only reporting endpoint data according to the needs of the study. This contrasts with traditional pathology, where specialists are usually provided with an entire pathology report, complete with the subject's medical history and related information such as blood work, X-rays and electronic medical records.

Current active areas of pathology support for clinical trials include HER2 gene status testing, papillary thyroid carcinoma, soft tissue sarcoma analysis, pap smears, and endometrial and gastrointestinal biopsies, to name a few. Beyond actual testing, opportunities to advance trial pathology are emerging from a process management perspective. For instance, tracking systems that leverage barcode scanning throughout the whole sample testing and travel stages are more routinely being incorporated into large clinical labs. At the same time, global central labs, in particular, are developing novel technology to streamline the data collection process and reduce errors, with the net goal of speeding up data delivery.

Sample Analysis

Advancing efficiencies in clinical trial pathology, however, will hinge on addressing the many challenges that still exist in sample analysis and exchange. One concern is meeting the

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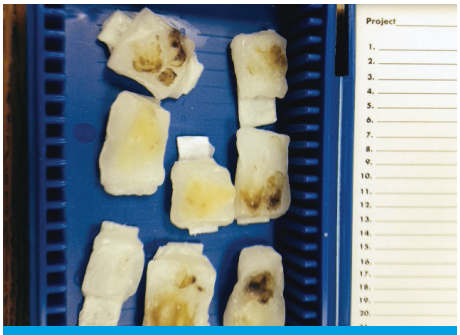

Figure 1: Paraffin-embedded tissue, not adhered to cassettes, submitted for pathologic complete response assessment

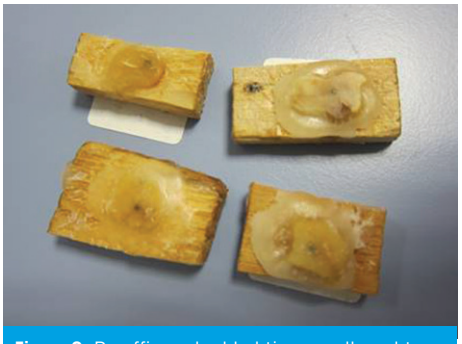

Figure 2: Paraffin-embedded tissue, adhered to blocks of wood in place of cassettes, submitted for HER2 analysis

tight turnaround time windows for patients to be screened and randomised into a study. This is especially true for subjects who are switching from the standard of care to a study drug; these patients are usually required to undergo a 'washout period' before they can start on the experimental treatment. It is crucial in these cases that the enrolment criteria for pathology clearly indicate that results must be turned around within a prescribed timeframe.

Furthermore, the requirement for expedited sample analysis is usually tied closely to disease invasiveness. For example, in trials targeting particularly advanced cancers, the maximum screening periods can sometimes be as little as two weeks.

Tissue Blocks

Another hurdle for central labs is being able to accurately predict how long it will take for the various referral labs to obtain tissue blocks. It is also vital that it is carefully considered where the blocks are coming from when collecting samples from global sites. Countries such as Russia and Ukraine require labs to file for import and export licences, because any tissue sent for analysis must be returned to the site. Other nations have rules in place that hinder delivery of clinical lab samples altogether. In China, due to regulations effectively prohibiting the export of human tissues, it may be necessary to fly the pathologist assigned in the US over to China to perform the reads at the end of the study to ensure consistency in the data, due to the interpretative nature of pathology.

Pathology results in trials can take a long time to obtain, relative to the schedule demands of the study. In some countries, if sites are not located in primary cities, courier transport of blocks can take at least three days. This requires labs, in many cases, to essentially perform testing in real-time.

An additional issue, specific to central labs, is attempting to make reads on tissue samples that have already been cut at the site's local lab. For example, in breast cancer, depending on the type of biopsy obtained – whether core needle or surgical – there may not be much, if any, tissue left to analyse.

Variability and Processing

Understanding the local lab's interpretation of the sample can present further difficulties. For instance, in the case of HER2 screening for a breast cancer trial, due to differing regulatory approved protocols around particular staining and interpretation methods, measures of gene level generated by the central lab and referral lab may not match.

Variability can also occur when both parties do not follow the American Society of Oncologists/ College of American Pathologists guidelines for IHC testing when conducting the readings. In either case, sponsors may be challenged to ensure accuracy when attempting to enrol patients with the same gene scale reading.

The quality of tissue processing at the site level is a key issue as well. Central labs prefer the samples embedded in paraffin and attached to cassettes; however, with sites located across the globe, it is not uncommon to receive the embedded tissue samples from certain countries that are attached to blocks of wood, or not attached to anything at all. This presents a test for the histotechnician, who must be skilled in handling global samples so they are able to re-embed them onto the necessary cassettes and still produce quality slides.

Ongoing Learning

True advances in the field are not defined solely by new analytical technologies or systems, but are largely borne from everyday learnings and experiences of working on multiple pathology trials. Refining problem-solving skills in clinical pathology will be critical as the number of global trials continues to increase.

Having pathologists on staff trained and certified in multiple branches of medicine can aid in these efforts, as well as benefit areas such as patient recruitment and trial access. With the reality that interpretation of pathology data can be variable, ongoing learning is essential to uncovering why separate readings of the same tissue do not align, and what can be done to close that gap.

Communication and knowledge sharing between labs and study sites is crucial too. For example, there are opportunities for labs, in certain instances, to advise sites on how a particular tissue should be obtained. In cases where a patient is having surgery during a study, the sponsor and central lab can provide guidance to the site's local lab on how exactly they want that biopsy handled and received. The ability of clinical pathologists to educate sites and sponsors on sample stability issues is also important, such as how long a sample will maintain optimal quality based on the specific staining performed. This knowledge could prove useful for sponsors in moving up scheduled tests in order to lessen the chance of skewed results due to a poor quality stain.

Though the technical and process management aspects of clinical trial pathology are numerous, there is little

argument that the field's interpretative nature still makes the practice very much an art as well as a science. Grounded in this belief, pathology will no doubt continue to play a significant role in the changing landscape of clinical research.

References

1. Personalised Medicine Diagnostics (flow cytometry, sepsis immunos, routine coagulation, psychiatric disorders, tumor markers, molecular blood typing and other testing), Renub Research, 2013. Visit: www.reportlinker.com/p01360928-summary/personalized-medicine-diagnostics-flow-cytometry-sepsis-immunos-routine-coagulation-psychiatric-disorders-tumor-markers-molecular-blood-typing-and-other-testing.html
2. 2015 Global Life Sciences Outlook: Adapting in an Era of Transformation. Deloitte, 2014. Visit: www2.deloitte.com/content/dam/deloitte/global/documents/life-sciences-health-care/gx-lshc-2015-life-sciences-report.pdf
3. The Personalized Medicine Market in 2015, MANA, January 2015. Visit: www.mana-llc.com/mana-blog/the-personalized-medicine-market-in-2015
4. Personalized medicine, targeted therapeutics and companion diagnostic market 2015: Strategic analysis of industry trends, technologies, participants and environment, PRNewswire, 17 February 2015. Visit: www.prnewswire.com/news-releases/personalized-medicine-targeted-therapeutics-and-companion-diagnostic-market-2015-strategic-analysis-of-industry-trends-technologies-participants-and-environment-300036965.html
5. The Case for Personalized Medicine, 4th Edition, Personalized Medicine Coalition, 2014. Visit: www.personalized medicinecoalition.org/Userfiles/PMC-corporate/file/pmc_the_case_for_personalized_medicine.pdf
6. Trends in Pathology and Laboratory Medicine, TechnoClin, 2014. Visit: http://technoclin.com/articles/trends-in-pathology-and-laboratory-medicine

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