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4D Path Prepping FDA Submission for AI-Enabled Breast Cancer Digital Pathology Product

By Kelsy Ketchum

NEW YORK – Although many pathologists still use traditional microscopic methods to interpret the clinical qualities of cancerous tumor tissue, digital pathology has seen increasing uptake in laboratories in recent years as more products become available and receive regulatory approval.

Digital pathology firms that harness artificial intelligence (AI), such as Paige and Proscia, have raised millions in private financing over the past year, and Inspirata has partnered with companies such as DeePathology to provide artificial intelligence-based digital pathology solutions.

Boston-based 4D Path is another company offering a digital pathology workflow that uses the power of AI to provide clinical diagnosis of tumor tissue and predictive indices that can help group patients for the correct therapy, according to 4D Path's Founder and Chief Scientist Satabhisa Mukhopadhyay.

The firm's cloud-based algorithm can extract microenvironmental dynamics, or "cell-to-cell talking," from images and translate that information into molecular immune profiles. That information includes the basics of histopathology, including the tumor's grade, but also includes molecular information, such as hormone receptor status, Mukhopadhyay said.

4D Path's first product, the 4D Q-plasia OncoReader Breast, received Breakthrough Device Designation from the US Food and Drug Administration last year and has been patented in the US. Breast cancer is the first focus, but far from the only – the company's Founder and CTO Tathagata Dasgupta said that it will expand into lung, ovarian, and skin cancer next.

4D Path takes scanned digital H&E-stained images of a biopsy or resection of a patient's tumor that have been sent to the cloud platform and returns in nearly real time a full patient profile that determines if cancer is present, the grade of the cancer, and molecular factors such as the hormone receptor status or the HER2 status. It then uses these factors to stratify patients according to what therapy would be best. Only the deidentified image is required — no patient health information is needed, Mukhopadhyay said.

While usually more information is provided from a resection than a biopsy, Mukhopadhyay said the 4D product can provide "resection-quality predictions" from a smaller biopsy image and reduce inaccuracy. In regular biopsies, there is usually between 15 percent and 30 percent inaccuracy, but in clinical trials 4D Path was able to get inaccuracy rates down to 5 percent compared to resection, she added.

In an image that contains many cells, those cells have different morphologies so a diagnostic system traditionally determines how many and what cell types are present. However, those cells are undergoing "many biological processes," Mukhopadhyay said, and are all in different phases. In the company's patented method, the algorithm extracts those morphologic factors and translates them to a mathematical map representing those processes. That map can then be directly connected to distortions in the biological pathways, which are translated to molecular profiles.

The hard work of creating the software, Mukhopadhyay said, was performing that translating and mapping to extract more data, and more importantly, "the right kind of data." Dasgupta added that when biological objects are going through processes, the morphology can be extracted to determine and quantify those changes. The interactions between cells are deformed because of a hazard, and by mapping the different hazards and the reasons for them, a mutation or biologic signature can be determined.

The main limitation for digital pathology products based on AI like these is the need to overcome variability, Mukhopadhyay said. There are two main kinds of variability: technological, which could include variation depending on differences in staining protocol, incubation time, or the use of different image scanners, and biological, which varies from patient to patient.

Two different patients could have the same morphology but different diseases, while two other patients may have the same disease with very different slides, Mukhopadhyay said. When an AI is trained on variable slides, the results can be skewed or jeopardized. The 4D Path algorithm quantifies and suppresses that technical variability and doesn't use colored slides as a way to reduce the technical variability that could come through color differences. It also has a proprietary image deprocessing module that first suppresses the additional technical variability and then processes the image to the next level, where the mapping occurs. The biological variability can then be quantified and patients can be sorted correctly based on that variability.

Because breast cancer is a very complex disease that is really "a collection of many diseases" and a "hard problem to crack," the firm focused on it first, Mukhopadhyay said. It also prioritized breast cancer because it "touches everyone," she continued.

Dasgupta also noted that because breast cancer patients tend to live longer with treatment, there is the opportunity to collect more follow-up data in the future and see if the algorithm's predictions are correct. The data "is very rich," which makes it easier to do clinical trials, he said. 4D Path partnered with the University of Leeds on three breast cancer clinical studies, analyzing images from more than 1,000 patients across multiple trials using the automated 4D Path workflow. The company has extended its partnership with the university until 2027 to expand trials into other cancers.

Clinical trials

Nic Orsi, a clinical lecturer at the University of Leeds and the chief pathologist for 4D Path, said that each trial addressed "slightly different permutations of the same diagnostic problem." One was based solely on detecting cancer from the H&E-stained images;

another focused on determining grade, HER2 gene amplifications and estrogen/progesterone receptor profiles specifically; and the third looks at the distinction between in situ or invasive disease.

The retrospective studies used Leeds Teaching Hospitals Trust's clinical histopathology archives to access samples, scan them, and run the images through the platform blind, with 4D Path's software providing the diagnosis and researchers checking it against the actual confirmed diagnosis of each sample determined through ancillary testing.

Orsi noted that the algorithm was "very good at identifying the presence of invasive cancer," which he called "the first step" towards moving onto doing further testing. The algorithm also had a high degree of accuracy in determining HER2 gene amplifications and performs well in terms of estrogen and progesterone receptor detection, he said.

The system can also identify different morphological subtypes, such as ductal carcinoma, which Orsi said looks mostly similar to what normal breast ducts should look like; lobular subtypes, where the cells lose adherence to each other and scatter more loosely; and mucinous subtypes where tumors produce a lot of mucin and look more diluted.

When the trials started, the company had to define the diagnostic boundaries for the algorithm, he said. The platform will provide a numerical output when it analyzes an image, but 4D Path had to decide which of the numbers on the output defined a particular type of cancer and what the range of the spread was, Orsi said.

Looking at the output of the algorithm, they used 20 cases with known outcomes to define which ranges of numbers correlated to cancer. It was a question of what range on the scale defines the type of cancer, Orsi said. They then ran the algorithm blind to see if it fulfilled the criteria and matched those defined boundaries, which it largely did, he said.

Measuring the grade of tumors, or how differentiated the new cells are from the original cells, could help determine how aggressive a tumor is, which helps determine the prognosis, Orsi said. Grade is identified by tubule formation, namely how architecturally normal the tumor is; pleomorphism, how abnormal cells look; and mitotic counts, measures of how proliferative a tumor is likely to be. Those factors are scored and then added, with the final number providing the grade.

There can be a lot of subjectivity in measuring the grade of a tumor, with Orsi saying there's a tendency to under-call grades. But 4D Path uses a surrogate scale that provides a continuous measure, rather than separating the final scores into grades 1, 2, 3, and 4, which removes subjectivity and cuts down on human error.

Orsi said the software had 97 percent concordance of the biopsy relative to the resection in the trials. Pathologists have about 80 percent concordance, he added. As surgeons move away from using resections, offering a high level of concordance with resections from a smaller biopsy sample is particularly useful, he said.

One issue in digital pathology that 4D Path's solution could address is the insufficient number of pathologists in the industry, Orsi said. Although there has been an increase in diagnostic demand for cancer as the population gets older, there isn't capacity within histopathology diagnostics to meet the rising need — only about 3 percent of histopathology departments in the UK are fully staffed, Orsi added.

4D Path could provide additional support for those pathologists by offering a faster result and a second opinion. It could also replace the ancillary tests, such as immunochemistry assays and in situ hybridization, done to double-check pathologists' work, which could decrease costs, he said. In places where there are limited pathologists available, such as rural areas, the tissue sample can be taken on site with the images processed remotely, which could help provide specialized knowledge that's not available in those areas. However, those departments would need to have a digitized set up to scan the images, he noted.

Andrew Hanby, a National Health Service consultant breast histopathologist at Leeds Teaching Hospital and a histopathology advisor on the trials, said 4D Path offers "a great deal of data that we can get so much more from." The system "will be able to squeeze so much more juice out of pathology and take it that step further, or many steps further, I'm hoping," he added.

Using this technology provides more reproducibility of results, and Hanby echoed Orsi's point that it can remove the subjectivity of determining a tumor's grade. It could also be used for new pathologists as a check of their work to help their training, Hanby noted.

A common hurdle faced by any digital pathology solution is the difficulty with introducing new technology to older pathologists who are used to using microscopes. These pathologists "generally are less keen to change habits of a lifetime," he said. Beyond that, however, he said he sees no major concerns. Right now, the results are as good as those of a human pathologist, but the goal is to make them even better by looking at broader populations of cases to allow for fine-tuning of the system, he said.

For the future, 4D Path is looking into large-scale research collaborations with pharmaceutical firms to help select and stratify patients in drug trials and develop companion diagnostics for different drugs.

Beyond pharma, the company plans to pursue full FDA clearance and CE marking, as well as regulatory approval in Brazil, Dasgupta said. The company added that it plans to submit for FDA clearance in the second or third quarter of 2021. When working on the validation trials for the FDA submission, the company plans to involve private payors to determine the health economics of the product, so the company doesn't have to perform a separate study. So far, 4D Path has raised $6.4 million from friends and family, but is in the process of looking for bigger scale venture capital funding, Dasgupta said.

He said the company is currently working on clinical trials for the skin cancer and ovarian cancer products.

Right now, 4D Path will offer three types of packages for laboratories depending on their needs and budgets, Mukhopadhyay said. One will be the simplest, with just basic clinical diagnosis of the tumor. One will provide more extensive clinical diagnosis, and the most complex will offer diagnosis and more specialized prognostic features. The most basic package will be for triage and rapid diagnosis, Dasgupta said, whereas the more complicated products will allow for "deep diving" into the tissue. The more basic packages will also likely have a turnaround time longer than a minute because there will be less computing power, Mukhopadhyay said.

The point of the solution is to offer a new approach to read biological information, he added. With it, pathologists "can extract more data than the human eye can see," and the solution "opens a completely new way of approaching biological data."