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Cytology digital workflow

Dr Bychkov: Good afternoon, I'm Dr Andrey Bychkov from Kamenda Medical Center, Japan. It's a great privilege to me to be able to present at this seminar organized by the European School of Oncology and the European Society of Pathology. Thank you very much for this opportunity to the organizing committee. We practice digital cytology on a regular basis since 2017. And I'm going to share with you our insights about the digital cytology workflow. So, this is the outline of my talk and I have no disclosures related to the content of this presentation. Let's start with the basics. Why going digital? This is my personal work-cloud, featuring the top areas of digital pathology. A key-word, number one to me, is telepathology which means accessing slides and making diagnosis remotely, a concept, which I call, anytime, anywhere. Number two is remote access to subspecialty, which is facilitated by telepathology. Number three is teaching, and there are many more opportunities shown here as individual awards. And this little bug in the right lower corner has recently emerged as another substantial reason to go digital, and all of you know about it. Current applications of digital pathology extend from education and research to clinical practice. Many of you, especially in academia, are much more familiar with education and research tools we have in digital pathology. But clinical application is much more important and difficult to implement. A use of digital pathology in clinical settings includes multiple aspects such as use for the primary diagnosis is already dealing with small-size specimens or larger-size surgical specimens. Also, for the consultation or second opinion either in-house or it could be remote and even international overseas. And more applications, for example, use of frozens, reporting frozens quality assurance, multidisciplinary team discussion, making digital archive. And finally, computer-assisted diagnosis automated with the help of AI tools. During the last decade, whole slide imaging became more affordable and widely accepted in pathology laboratories. And once again, this drive was much accelerated by the ongoing COVID pandemic. However, adoption of telecytology in the routine pathology workload is challenging due to technical limitations. And let's look and read about all these limitations. This is a very important part of my presentation today. This limitation includes inherent challenges of whole slide images, whether cytology or not cytology such as counting time, such as storage needs due to large file size, adjustment of the workflow and training requirements, especially for your technicians and lack of interoperability and multiple vendors. There's a need of IT support. There's the high cost of the digital technology today, and there are no more limited validation studies. So, once again, these were inherent challenges of any whole slide imaging, not only digital cytology. But these are unique challenges posed by

digital cytology itself. And these challenges are related to 3D structure, which requires advanced scanning mode, and which is very slow at higher magnification up to one hour per one slide direct smear. It's memory consuming. On top of that, there are focus challenges. It's difficult to do automated focusing in thick smears and low cellularity specimens. And also, on pen-marked glass slides, difficult to deal with smears extending beyond coverslips and scanning area. That's why we recommend using LBC for digital cytology. We have workflow challenges, cytology-specific workflow challenges. For example, we need to navigate slides for screening and interpretation. This can be completely different steps. We need to handle slides with multiple stains. And another challenge is posed by the rapid on-site evaluation. Here, I show you a comparison of histologic on the left and cytologic slide on the right. Histologic specimen is just 4 to 6 microns in thickness. It's been relatively flat and therefore, having all the cells tissue specimen position in a single plate, all cytologic specimen is up to 30 microns in thickness from the coverslip to the glass and cells position anywhere. When I say cells position anywhere, I particularly meant at different planes with regard to the focus. 3D issue in cytology is basically defined by thickness of the smear, a presence of 3D cell clusters, and important that these 3D structures are diagnostically significant. To manage the 3D issue in whole slide imaging, we can use two options. Number one is advanced scanning mode. And number two is the video microscopy. Advanced scanning mode could be either Z-stacking or extended focus, or extended depth of field model. Regarding video microscopy, all of you know well, this is where microscope is equipped with a digital camera, and then the video is streamed on the screen. This can be edited by screen sharing. This can be edited by remote control, and this approach is known as robotic microscopy. Finally, Z-axis video can be recorded and compressed in WSI format. Now let me brief you about these two important advanced scanning modes. Z-stacking. Z-stacking is when images captured from multiple planes along the Z-axis above and below the optimal focal plane are used to create the 3D structure or Z-stack image. There are several layers or stacks, from 5 to 15 usually, and these allow you to zoom-up and down different planes to find cells or structures that are optimally focused in the regions of interest. Extended focus mode, also known as EDF, extended depth of field, is a multi-plane scanning with integration of the best focused image at each tile into a final single plane file. This is perfectly illustrated in the image I borrowed from a book chapter by David Wilbur. And only is the best focal style from each layer are combined in a composite image which is ultimately flat. Here's an example of the same cell cluster, captured with single plane on the left versus multiple planes combined in all- in-one EDF mode. A lot of stuff is out of focus on the left, but perfectly seen in the EDF mode. Another slide. This is Z-stack in action. We've crossed about 10 single plane layers here on the left and get an overall impression of three-dimensional cell cluster. Many of the cameras in the market are able to do this technique. This is EDF in action. All cells initially dispersed along Z-axis are brought to a single plane. We get no 3D rendering here, but are able to see all the fine details in color for diagnosis. And this is the actual slide produced by a Motic's camera. This summary table, finally, shows comparison of the two modes. Advantage of Z-stacking is ability to evaluate a 3D structure. And disadvantages are longer scanning time and larger file size. Advantages of extended focus mode is relatively a large size and having all areas in the focus. The disadvantages, that no 3D structure finally revealed. And surprisingly scanning time it's similar to Z-stack scan. Let's move on to the use cases of digital cytology. Potential applications for the whole slide imaging inside cytopathology are multiple and are listed here. The most desirable is a primary diagnosis by telecytology. Another one is remote real-time on-site evaluation used, for example, for ROSE, remote second-opinion consultation. We have various educational activities that could be run through the digital cytology. Also, quality assurance, archiving interesting cases, and ultimately, research with image analysis. But due to the technical limitations explained in the previous slides, at the moment, there are only a few reports available on successful implementation of digital cytology. And these were mainly limited to remote rapid on-site evaluation while other uses of digital cytology are largely unexplored. And here, an example for you. I just compiled recent talks and publications of digital cytology, top conferences, and then the leading cytology journals. This is at USCAP this year, one in there is from Pathology Visions, regional studies in American and British cytology journals. Even Pathology Outlines. You may see that all these sources are reporting that all digital cytology is essentially limited to the ROSE. And this creates an impression that

telecytology is used only for remote rapid evaluation, which I believe is a wrong impression. And one of my missions today is to prove that the applications of digital cytology are far beyond rapid evaluations. And now, after such a long introduction, I would like to share our own experience with implementing diagnostic digital cytology into daily clinical practice. Our digital pathology network, connecting academic institution, Nagasaki university and large-scale hospital, Kameda Medical Center, which I belong, and several independent and affiliated laboratories, was established in 2017. And this is what we are having today. There are two hubs with a distance of 1000 kilometers in between. And our network includes about 40 pathologists, both general, specialized, also training, full-time, consulting who are responsible for diagnosis of over 40,000 histopathology cases per year. In 2018, we achieved a hundred percent digital workflow for biopsies and surgeries. Speaking about technical setup, we use multi-vendor solution, both low-cost and high-volume. Here on the left is an example of the hardware, of scanner and workstations we are using. And on the right is the software, different brands of the software, including those used for viewer, for cloud storage, for web communication and for image analysis. So, since we are operating as a network, this is a key-slide for me, how to make all those remote locations, over 1000 kilometers in distance connected? And this is a key question when you operate as a network. That communication is the answer and is a backbone of whole our system. We connect institutes and rooms by Webex in an open secure online channel from 8:00 AM to 8:00 PM, which made us able to held regular sign-out sessions, diagnostic sign-out sessions. And we are fully accessible for consultation and remote frozen service. This is our sign-out session schematically where real chosen slides are shared on the screen and discussed. This particular session had a teaching mission, that's why many people are involved. We can view simultaneous education and diagnostic double-check. And I just realized that this slide is well-matched with all the proceeding talks in our session. So, let's call this as a camera digital workflow showing here. Now, let's get back to the cytology track. Kameda Medical center, with approximately 22,000 cytopathology cases annually, served as a model institution for implementing digital cytology. Important that in order to adopt digital cytology, and successfully, we had the switch workflow to be LDC-based, and we used SurePath here. Here is a breakdown by organ system of our cases, and sampling adequacy in our institution was approaching 99%. Our routine cytologic workflow includes two-steps screening by cytotechs followed by sign-out by a pathologist certified in cytopathology. And I believe this is very similar to what all of you are doing in your laboratories as well. Available equipment for digital cytology, which we are viewing here. It is a simple microscope with the live video output. There is a robotic microscope by Sakura. It's a Panoptiq microscopic digital imaging platform, which is based on a high-resolution video camera and software able to convert video stream into the whole slide imaging format. And finally, there is a slides camera with EDF and Z-stack modes. So, at this moment, we know exiting the workflow, which I just showed minutes ago, and we are familiar with the equipment. And now, it's the right time to get back to the slide with use cases of digital cytology and make only two questions, can we, do it? And do we need it? And let's go one by one. Primary diagnosis or telecytology of the specimens. Do we need it? Absolutely. Can we, do it? I mark it as a plus-minus, because technically we can digitize all the stacks of this multi-stack workflow. Rapid on-site evaluation. We can do it, but we don't need it, actually, because of the very low-rate of inadequate sampling in our hospital. Now regarding education, archiving, research both answers are, yes. Since none of the above-mentioned technical approaches could substitute a screening step efficiently at the moment, we decided that digital solutions could be more helpful at the later stages of cytologic workflow, such as double-check of positive cases and sign-out by cytotechnologists. In addition, more recently, we faced the lack of expert cytopathologists who are not available at each of our locations. So, that was a perfect step to introduce the digital cytology. As a solution, we introduced sign-out of cytologic cases using live digital microscope operated by a cytotechnologist, which allow reviewing slides remotely by a pathologist via video streaming. Schematically, there is a cytotech in the lab, usually accompanied by a junior resident who's streaming a digital slide, particularly suspicious of positive cell clusters to the cytotechnologist located in the central office, with the aim to confirm or validate diagnosis. For these tasks, we use Panoptiq platform which, once again, is based on the high-resolution video camera mounted on any microscope, and software are able to convert this video stream into the whole slide image format such as

SAS. Our remote cytologic sign-out was started back in 2018 and covers something like 25 to 30 cases per week, I will say that more than 70% of positive cases today are currently signed-out remotely. After devising trialing and fully deploying this approach came to be a solid base for us on use cases. For instance, we provide cytologic correlation to support the virtual slide-based sign-out of histopathological specimens, where we merge cytology and histopathology. We also support radiology pathology conference where both cytology, histology and radiology are correlated for diagnostic and educational purposes. So, about 20 cases, biopsy cases, per week are correlated and aligned with cytology and one or two cases are outsourced for discussion with radiologists online. And in addition, positive cytology cases are archived for integration into NIS, educational purposes and for perspective AI studies. Digital cytology archive is prepared by easier approach such as Z-axis video and EDF mode. And just to make sure, prior to a wide deployment, we did perform validation both for the primary diagnosis and for consultation, which were published a while ago in Cancer Cytopathology and Journal of American Society of Cytopathology. So, we wrap up. While the adoption of digital mode for the primary cytologic diagnosis is limited, we recommend other uses of digital cytology for practical and educational purposes. Since 2018, we regularly use digital cytology for remote sign-out, providing histological and radiological correlations, and archiving virtual slides, which proved to be successful in our setting. Our unique experience may be used as a model for adoption by other institutions like your institutions. With that I'm going to close my talk. Remember that we have several labs here in Japan, and you're welcome to visit any of our facilities to learn about digital pathology and exchanging experience. Thank you very much for attending. And I look forward to our Q&A sessions several minutes later.