Philippine Society of Pathologists, Inc.

Vol. 3 No. 2 November 2018
ISSN 2507-8364 (Online)

PHILIPPINE JOURNAL OF PATHOLOGY

The Official Journal of the Philippine Society of Pathologists, Inc.

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IMAGES IN PATHOLOGY

Ameloblastic Fibro-Odontoma
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Philippine Journal of Pathology
Vol. 3 No. 2 November 2018 | ISSN 2507-8364 (Online)
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PHILIPPINE JOURNAL OF PATHOLOGY

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Greetings to our PJP readers,

This is now our 2nd issue for 2018 and the 5th issue since 2016. I hope everyone is pleased with our issues and I hope our pathologists, especially our trainees, are inspired to write articles, submit their researches and case reports. This journal is your venue for your works to be seen and read.

Please take time to read our journal and be inspired to contribute.

Bernadette R. Espiritu, MD, FPSP, MMHoA, MIAC
President, Philippine Society of Pathologists, Inc.

Just Before Dawn

Publication is research work's endpoint. Unless we publish our work (i.e., "to make public"), our outputs will not be included in the body of scientific literature, will neither be cited nor acknowledged, will be lost knowledge and information, and ultimately cannot be built upon by future researchers. Publication is permanence and is an imperative for a professional society like the Philippine Society of Pathologists.

For us Filipino pathologists, the publication of our local data, is an issue that can be addressed systematically, purposefully, and comprehensively.

First, there must be recognition from our leaders on the need for evidence on which to base our practice as laboratorians and laboratory managers, and, from there, investment of time, effort, and funding.

Second, there must be concrete planning of the steps to take, to get us from the status quo to what should be. The Committee on Research of PSP and Board of Pathology are in the best position to do this, through purposeful capacity building of our young pathologists on the necessary research competencies–from grant proposal writing to research methodologies, from data analysis to research writing–to generate the results that we need. We can consider publication and not mere completion of research, as a requirement for residents and diplomates.

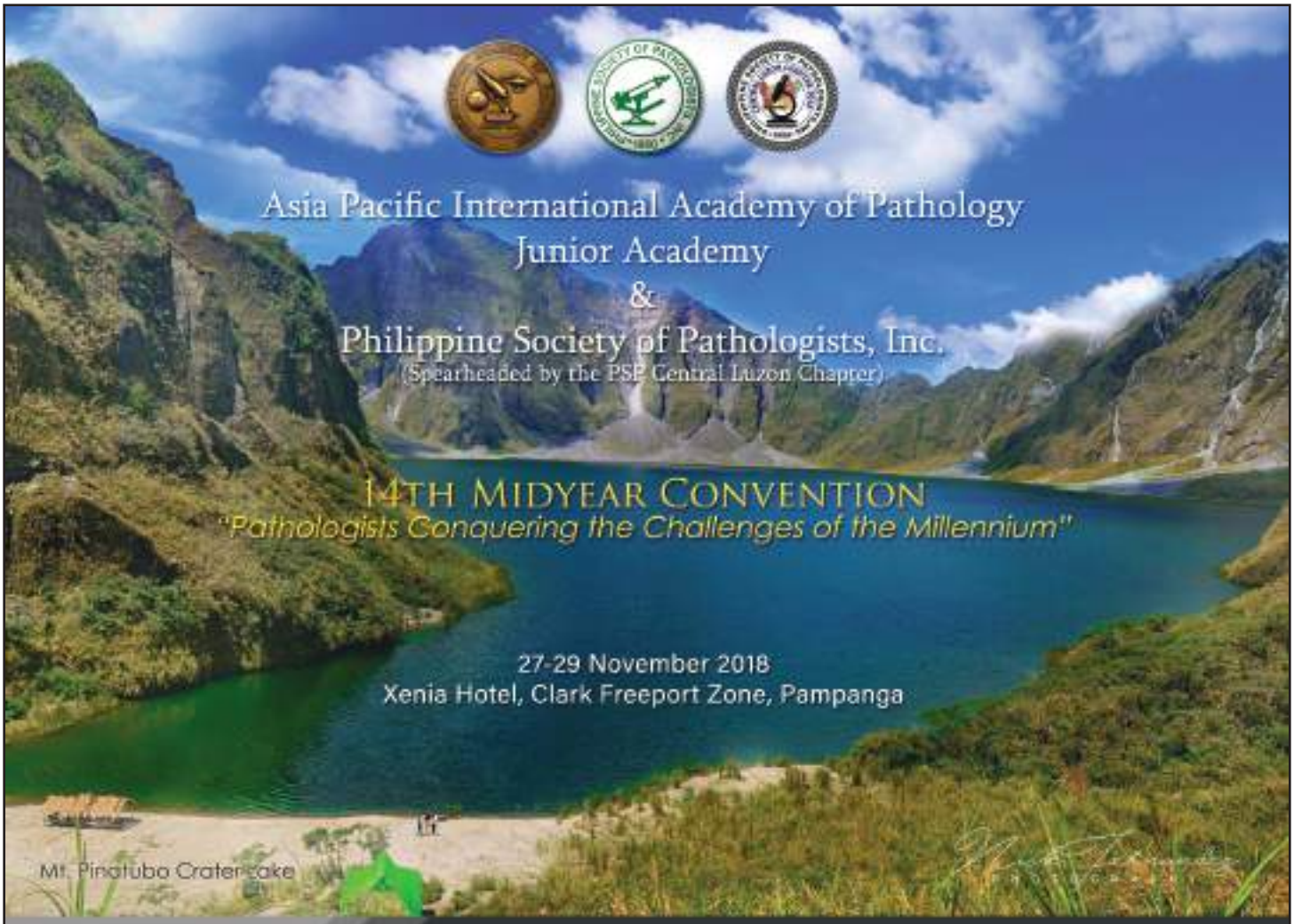
Third, the society can support the research consortia being organized by the pathology training institutions, in order to stimulate research questions and catalyze collaborations. I must thank PSP for her recognition of PJP as a high-quality platform for pathology research and her continued support to the operations of the journal. But the society can do more, by investing in medium- and long-term research agenda setting, as well as, looking into establishment of grant schemes to motivate our pathologists-in-training to go into research.

Thomas Fuller, a historian and theologian, was the first one to have said that "the night is darkest, just before dawn," which reminds us that things get worse, before they get better, and more importantly, that even in adverse circumstances, there is hope.

We are on our way. We will get there.

Amado O. Tandoc III, MD, FPSP
Editor-in-Chief

https://doi.org/10.21141/PJP.2018.008



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NOVEMBER 27 TUESDAY

08:30-08:40 Opening Remarks
Dr. Bernadette Espiritu
PSP President

08:40-08:50 Opening Remarks
Puay Hoon Tan
Convener, AAPAP

08:50-10:00 Molecular Pathology for Anatomical Pathologists
Stephen Fox

10:00-10:30 Coffee Break

10:30-11:10 Difficult Issues in Papillary Lesions of the Breast
Puay Hoon Tan

11:10-11:50 The Role of IHS in Breast Cancer Management
Gary Tse

11:50-12:30 PDL1 Assessment in Non-small Cell Lung Cancer
Stephen Fox

12:30-01:30 Lunch Break

01:30-02:10 What WHO 2016 has Not Solved for Adult Gliomas
Ho-Keung Ng

02:10-02:50 Can Pediatric Low Grade Gliomas Really Be Diagnosed By Microscopy Alone?
Ho-Keung Ng

02:50-03:30 Sclerosing Breast Lesions
Gary Tse

03:30-04:00 Coffee Break

04:00-04:40 Fibroepithelial Lesions - A 2018 Update
Puay Hoon Tan

04:40-05:20 How Can A Regular Lab Do Molecular Diagnostics of Pediatric Brain Tumors?
Ho-Keung Ng

06:30 Fellowship Night
Theme: Filipino Cultural Night

NOVEMBER 28 WEDNESDAY

09:00-09:40 Algorithmic Approach for the Diagnosis of Fungal Infections
Isaac Solomon

09:40-10:20 Effective Utilization of Molecular Diagnostics in Infectious Disease Pathology
Isaac Solomon

10:20-11:00 Endometrial Hyperplasia to Carcinomas
Naila Kayani

11:00-11:30 Coffee Break

11:30-12:10 Cytology and Pathology of Salivary Gland Tumors
Jen-Fan Hang

12:10-12:50 Emerging and Re-emerging Viral Infections in the 21st Century
Isaac Solomon

12:50-02:00 Lunch Break

02:00-02:40 Updates of WHO Classification and AJCC Staging of Head and Neck Tumors
Jen-Fan Hang

02:40-03:20 Mesenchymal Tumors of the Uterus
Naila Kayani

03:20-04:00 Common Ovarian Surface Epithelial Tumors -Histological and Immunohistochemical Assessment
Naila Kayani

04:00-04:10 Closing Remarks
Course Directors

NOVEMBER 29 THURSDAY

08:30-09:15 Investing in People: Knowing the Standards in Personnel Management
Ms. Marides Distor

09:15-10:00 Risk Management in the Laboratory
Mr. Brian Eclarinal

10:00-10:15 Coffee Break

10:15-11:00 Change Management
Atty. Josephine Fernandez

11:00-11:45 Workshop: Application of Change Management Tools

11:45-12:45 Lunch Break

12:45-01:45 Part I- Financial Management and Metrics: Making Sense of Financial Jargon
Ms. Piya Tan

01:45-02:45 Workshop: ROI, Break Even Points and More

02:45-03:30 Part II- Financial Management and Metrics: Supply Chain Management
Ma. Carla G. Nanong

03:30-03:45 Coffee Break

03:45-04:30 Part III- Financial Decision Making for the Pathologists- Financial Strategies for Laboratories
Mr. Luigi Bamas

04:30-5:00 Closing Ceremonies

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OPEN ACCESS – FEATURE ARTICLE

Digital Pathology: An Innovative Approach to Medical Education

Leonisa Sagun[1,2] and Randell Arias[1]

[1]*Division of Laboratory Medicine, Philippine Heart Center*
[2]*Department of Pathology, Centro Escolar University-Manila School of Medicine*

ABSTRACT

Pathology, a basic science course in medical schools is a highly visual subject that requires examination of tissues using a microscope. With progressive technological advancements, the use of time-tested optical microscopes in teaching is seemingly slowly replaced by virtual microscopy that many medical schools in developed countries proved its numerous advantages. In our setting, digital pathology is not yet fully integrated in medical school. Although a few medical institutions in the country may have started this technology, there are still a lot to explore with virtual microscopy that will unlock its full potential of revolutionizing medical education in the future.

Key words: digital pathology, virtual microscopy, medical education, pathology education

ISSN 2507-8364 (Online)
Printed in the Philippines.

Received: 15 November 2018.
Accepted: 20 November 2018.
Published online first: 22 November 2018.
https://doi.org/10.21141/PJP.2018.009

Corresponding author: Randell S. Arias, MD
Email: docninoy@yahoo.com
ORCID: https://orcid.org/0000-0002-8482-0852

INTRODUCTION

Pathology is the medical discipline that provides a scientific foundation for medical practice. It is a required basic science course in medical school, and is often the first introduction to human disease processes.[1] Compared with other basic sciences, pathology is a visual subject that is based in part on histopathologic examination of tissues which is important to understanding basic mechanisms of disease processes.

The microscope has been the most widely used instrument in pathology education and until now, is still a mainstay in the classrooms and laboratories of pathologists. However, pathology is under a digital revolution enabled by virtual microscopy – the practice of converting glass microscope slides to high-resolution, whole-slide digital images[2] that some recent studies have demonstrated a decrease in the use of traditional microscopes in medical schools, mainly as a result of current developments in the curriculum as well as some disadvantages of the technique itself.[3]

Whole slide imaging (WSI), also known as digital pathology or virtual pathology, is a technology that involves high-speed, high-resolution digital acquisition of images representing entire stained tissue sections from glass slides in a format that allows them to be viewed by a pathologist on a computer monitor, where the image – often referred to as the 'whole slide image' or digitized slide' can be magnified and navigated spatially in much the same way as standard microscopy.[4] In addition, the digital slide images can be viewed across a network, including the Internet, using specialized viewing software[2] – a potential area for accurate and timely diagnosis in actual pathology practice compared with traditional methods.

Significant technological advancements of digitizing slides and the development of workflow tools that facilitate remote viewing and analysis are likewise enabling pathologists to substantially change how they learn and practice their profession.[2] With the emergence of digital pathology over the past several years, there is

Table 1. Benefits of digital pathology/virtual microscopy versus traditional microscopy

Digital Pathology/Virtual Microscopy	Traditional Microscopy
Images can be standardized	Variability of histologic sections
Image quality can be maintained indefinitely	Variability of histologic sections
Multiple annotation can be done	None (except, pointer an/or pen marks)
Easier storage and retrieval	Requires physical space for storage of both microscopes and glass slide sets
Images of rare cases can be stored indefinitely	Glass slides of rare cases cannot be duplicated and made available
Cost-effective over time	Maintenance and replacement of microscopes and glass slide sets are costly
Convenient for both teacher and student	Time-consuming during preparation and actual lecture

an opportunity to revolutionize the way teaching and learning are done in medical schools in the country and would create opportunities beyond classroom teaching.

TRENDS IN IMPLEMENTATION

Digital pathology has already been implemented in many medical schools in the United States and other developed countries and has been shown to provide advantages compared with the usual traditional method of teaching histology and pathology courses.[5,6,7,8] A few of developing countries has utilized the digital pathology in the form of telepathology in clinical practice.[9,10] Telepathology is the electronic multimedia communication across a network of pathology-related information, between 2 or more locations for use – cases between pathologists and/or qualified laboratory personnel, and may include involvement by clinicians and/or patients.[11] Several journals reported the use of digital pathology in the form of telepathology in education,[12] second-opinion consultations,[13,14] and primary diagnosis.[15,16,17] Success in the implementation of virtual microscopy has been documented in graduate education in medical,[18,19,20] dental[21] and veterinary schools.[22] In addition, the US Food and Drug Administration approval of whole slide imaging (Philips IntelliSite Pathology Solution) for primary diagnosis in surgical pathology in 2017 marked a significant evolution of digital pathology.[23] If the current trend continues, the implementation of virtual microscopy may eventually make the time-tested microscope a relic in medical education, and possibly in pathology laboratories.

THE LEARNING ENVIRONMENT

The general pathology course in medical education includes different elements, each with different learning goals. In our experience, these elements include lectures, virtual microscopy lessons and small group discussions. The virtual microscopy session involves 1 teacher per 12 students wherein selected microscopy specimens are scrutinized and allowing students to interact actively. The small group discussions include case studies wherein theory from lectures are combined with information from textbooks, microscopy and clinical data (clinical correlation). Proper alignment of these study elements would allow microscopy to be seamlessly integrated in all aspects of the course, improving microscopy knowledge and performance of the students. From this pioneering experience, we utilized digital pathology in classroom teaching that favors student-centered, self-directed learning. This new framework based on platforms familiar with twenty-first century students will change how they learn pathology – a transition from seeing actual gross and microscopic specimens to looking at images from Web-based resources.

PRACTICAL BENEFITS OVER CONVENTIONAL MICROSCOPY

There are many advantages to using digital pathology or virtual microscopy than with traditional microscope glass slides (Table 1). Digital images can be standardized, with the potential for image enhancement, so that all students will study the exact same tissue section. Microscopic sections on glass slides show variability with regards to quality and content[24] which may often be incomplete and not identical leading to discrepancies in testing and scores of students. These variabilities can be substantially eliminated with digital imaging. Compared to glass slides that are prone to fading, breaking and loss over time, the quality of the image can also be indefinitely maintained with digital pathology.[25] In addition, rare cases of glass slides cannot be duplicated and made available for the students.

Another very helpful aspect of virtual microscopy is that digital images of microscopic glass slides on a computer screen have panning and zooming capabilities simulating moving the stage and the low to high power magnification of an optical microscope.[26] The digital image has a thumbnail image from which the students can always refer to when viewing the digital slides at a higher magnification for proper orientation of histologic sections (Figure 1).[3]

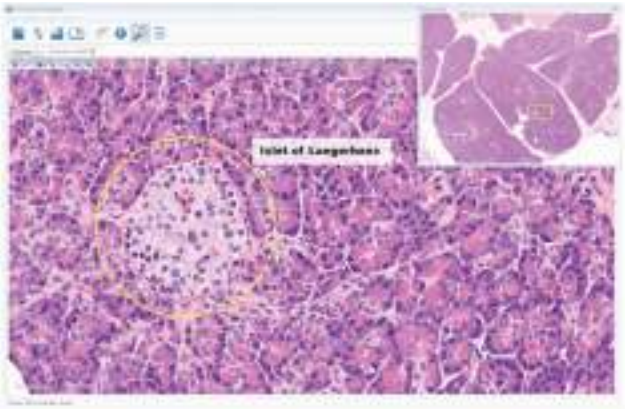

Figure 1. Virtual Microscopy Platform. Screenshot of the digital slide viewer in the virtual microscopy platform showing the pancreas [Online image] (2018). *Retrieved from https://www.mbfbioscience.com/iowavirtualslidebox.*

Conventional microscope glass slides cannot be easily annotated with any precision, and rely on crude techniques like pen-marking/"dotting" (Figure 2) and utilizing eyepiece with pointer for highlighting a certain area in the field (Figure 3). Multiple annotations (arrows, circles, texts, etc.) can be placed exactly where needed in the digital images.[19]

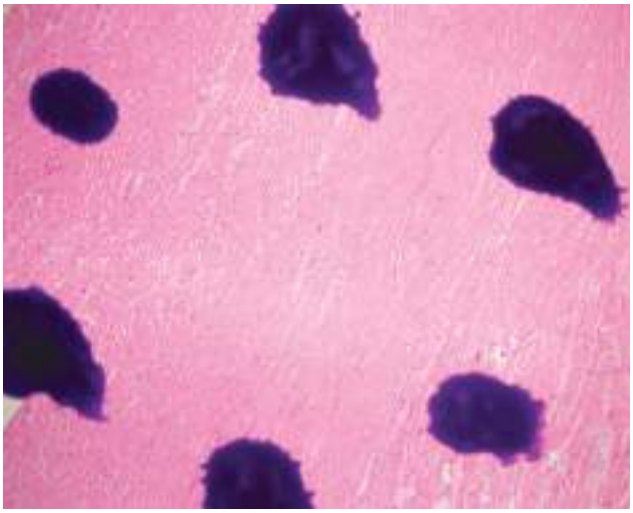

Figure 2. Crude technique of pen-marking or "dotting" on a microscope glass slide. This is a photomicrograph showing the "dotted" area which highlights an acute myocardial infarction (H&E, 40X).

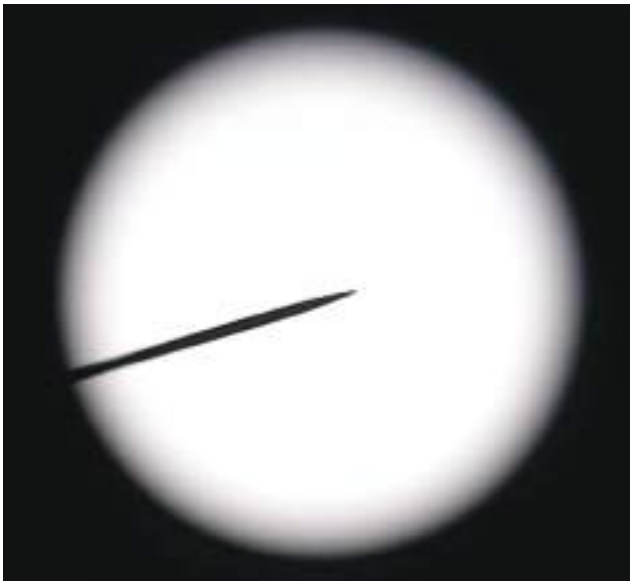

Figure 3. Microscope eyepiece with pointer. This technique is more common in the traditional microscopy classroom to point structure of interest [Online image] (2018). *Retrieved from https://www.amscope.com/wf10x-microscope-eyepiece-with-pointer-23mm.html.*

Aside from these benefits, the time used for setting up the educational sessions and actual teaching process are much less compared to traditional microscopy, hence giving students more time to learn. The use of the microscopes is often limited to the working hours of the faculty, requiring the students to be physically at school for self review.[19]

With digital pathology where whole-slide images are loaded onto a web-based server, study can occur wherever and whenever the student wishes.[25] Finally, storage and maintenance of microscopes and glass slides sets are cumbersome and require significant expenses.[2] Digital images can be easily stored in server memory or computer disks which provides smooth retrieval.

IMPACT ON STUDENT LEARNING

The possibility of providing students with all the information they need electronically has been an idealized concept for many years.[27] Web-based resources including social media have shown benefits to supplement education in a cost-effective way. This was certainly one of the reasons for the positive attitude of the students toward digital pathology. Several studies have proven that the majority of students believe that the use of digital slides enhanced their ability to learn.[24,28]

Virtual microscopy has not only been reported to improve the student learning process, but it has also been shown to improve their cooperation skills, communication abilities and self-confidence.[29] However, some students still find it important for them to be proficient in using the traditional method of viewing the glass slides. The sense of fulfillment of manually operating the microscope – focusing the image, navigating the slides and changing objectives – cannot be satisfied by digital slides. In our setting, the extent of what digital pathology can offer for student learning has yet to be explored which includes remotely reviewing the digital images anytime, anywhere.

IMPACT ON TEACHING

The transition from conventional to virtual microscopy presents certain challenges for teachers. The methods of preparing and delivering the lessons changed. Teachers could now prepare lessons at home on a personal computer without requiring access to a microscope.

In addition, there will no longer be any time-consuming, hands-on microscope work during lessons which could create more time for reviewing specimens with the students.[27] Digital pathology has enabled each teacher or course director to customize a collection of scanned slide specimens to suit particular needs. Teachers regarded this flexibility as a positive aspect of virtual microscopy.[27]

CHALLENGES IN IMPLEMENTATION

Implementing digital microscopy in medical education may not pose crucial challenges as in diagnostic practice. Unlike in medical education, digital microscopy in the actual practice of pathology requires several important considerations, of which quality slides that are cut and stained properly are a crucial step.

Aside from these, barcode labelling of slides for accurate identification of data entry into database, slide scanning, integration of the scanned data and image-viewing applications into the laboratory and hospital's information system and the technological infrastructure enabling image transfers must be taken into account.[26]

Digital slides used in teaching are customized according to the topic of discussion. These may not necessarily come from the original scanned glass slides from the Histopathology Section, but may be retrieved from image-viewing applications or pre-loaded digital images by the system provider.

Establishing a digital microscopy laboratory is initially an expensive project, but may eventually become economical than traditional microscopy which relates to additional costs in the storage and maintenance of microscopes and glass slides sets. Dee et al., calculated the cost of a microscope laboratory for 50 students to be about $100,000 per year, which approaches the complete start-up costs for virtual microscopy, including purchase of a virtual slide scanner.[30]

In low resource areas such as in our setting, the challenges are more apparent. Access to the Internet on academic networks is often slow and expensive. Aside from the cost, other barriers include the limited student access to computer workstations especially after class hours, technical aspects such as unreliable electrical power and adverse weather events which could disrupt telecommunications.[31]

Teacher-student interaction is also a concern. It would seem like virtual microscopy would decrease the dynamic interaction between teachers and students. However, in truth, this technology enabled the students to learn pathology in a more interactive and stimulating manner.

OPPORTUNITIES FOR DIGITAL PATHOLOGY IN EDUCATION

Although the classroom offers a high utility environment for digital pathology in medical education, many other education-related areas also benefit from the use of digital pathology, including decision support, digital slide conferences, proficiency testing and quality assurance.[2] The possibility of creating a repository of digital slides by pathologists over time can be helpful in decision support.[2]

The accessibility of digital pathology makes it easier to present in seminars, symposia and conferences. Of these scientific presentations, clinicopathologic conference, tumor boards and morbidity/mortality/autopsy audits are among the most commonly encountered meetings by a medical student. Digital slide conferences conducted via the Internet allow multiple participants to view the digital slides simultaneously, and in real-time.[2]

Digital pathology can be utilized in training and education in the form of proficiency testing in other fields of anatomic pathology. It has been shown that proficiency testing in gynecologic cytopathology ("virtual Pap tests") is feasible.[32] Similar with proficiency testing, the cost and difficulty of glass slides logistics in quality assurance (QA) practices is one of the drawbacks of traditional microscopy. With digital pathology, it is simple to make digital slides accessible to other facilities and organizations for QA programs.[2]

Finally, digital pathology can be utilized in other learning courses such as microbiology, hematology, histology, cytology and clinical microscopy (urine and body fluids) and integrated in online platforms showing educational videos and slide navigation of particular topics in medicine.

CONCLUSION

Digital pathology is a powerful educational tool that could effectively replace the traditional standard methods of teaching and learning pathology. It provides mobility and convenience to medical students and teachers alike. While majority of the medical schools in the country still consider microscopes and glass slides inevitable in pathology education, we believe that in the coming years, digital pathology will be eventually integrated not only in pathology and histology curricula, but also in other courses requiring microscopy. It will potentially revolutionize medical education and create several opportunities beyond classroom teaching.

STATEMENT OF AUTHORSHIP

All authors certified fulfillment of ICMJE authorship criteria.

AUTHOR DISCLOSURE

The authors declared no conflict of interest.

FUNDING SOURCE

None.

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OPEN ACCESS – ORIGINAL ARTICLE

Interobserver Variability of Gleason Score and Completeness of Histopathology Report in Prostatic Adenocarcinoma in Prostate Needle Biopsy Specimens among General Pathologists in a Multi-institutional Setting

Anne Lizbeth Valdez and Jeffrey So

St. Luke's Medical Center, Quezon City, Philippines

ABSTRACT

Introduction. Gleason score, the most widely used grading system for prostatic adenocarcinoma, is the most powerful predictor of patient's clinical outcome and is used to customize treatment strategies. It possesses an inherent degree of subjectivity, as inter-observer and intra-observer variability does exist. Moreover, there are currently no structured histopathology report guidelines for prostate needle biopsies in our setting, making relevant information overlooked by pathologists and interpretation of report between laboratories challenging.

Objective. With these in mind, we sought to study the interobserver variability of Gleason score and completeness of histopathology report in prostate needle biopsy specimens.

Methodology. A set of 19 prostate needle biopsy slides was sent to 18 general pathologists from different institutions in the Philippines for histopathologic analysis of Gleason scores and completeness of reporting. The interobserver agreement of each pathologist will be evaluated using Spearman's rank correlation coefficient.

Results. Overall, there was moderate correlation between the interobserver's Gleason score and Gleason grade group. Low to moderate correlation was seen in primary grade while negligible correlation was seen in secondary grade. Best agreement was seen in poorly differentiated neoplasms. Undergrading was more common than overgrading. Most respondents gave an incomplete histopathology report.

Conclusion. There is an overall moderate correlation between Gleason score. A non-standardized histopathology report is currently used, leaving out relevant histopathologic findings.

Key words: prostate, prostate cancer, urology

ISSN 2507-8364 (Online)
Printed in the Philippines.

Received: 11 July 2018.
Accepted: 2 September 2018.
Published online first: 16 September 2018.
https://doi.org/10.21141/PJP.2018.010

Corresponding author: Anne Lizbeth B. Valdez, MD
E-mail: anne_lizbeth@yahoo.com
ORCID: https://orcid.org/0000-0001-5863-5875

INTRODUCTION

Gleason score is the most widely used grading system for prostatic adenocarcinoma. Inevitably, like all other grading systems, it is flawed by some degree of interobserver and intraobserver variability.[1] Although this grading system has undergone significant revisions for the past years, it still continues to have deficiencies that can potentially impact patient care.

Gleason score is the most powerful predictor of patient's clinical outcome and is a major determinant in customizing treatment strategies that is most appropriate for a patient. It is utilized to tailor-fit post biopsy treatment, plan for the type of radiation therapy and whether to administer hormonal therapy with radiation therapy. Patients with Gleason scores of <6 may benefit from watchful waiting and surveillance as initial management.[1] The presence of high-grade Gleason pattern (Gleason pattern 4 or 5) harbors the greatest risk for metastasis and treatment failure. Thus, discordance in Gleason scoring, albeit small, will have a dramatic effect on risk stratification and clinical management.

It has been observed that general pathologists more frequently underscore than over score, with a natural tendency to assign low Gleason pattern in such small core needle biopsies. In a study done by RV Singh et al.,[2] Gleason score 7 was identified as an area of difficulty as 14 of 63 readings (22%) were underscored. The differences centered on the assessment of small areas of fused and separate glands and fused small irregular glands. This has lead to the inappropriate assignment of Gleason score 6 and probable suboptimal patient management as a consequence. In the same study, assignment of Gleason pattern 4 and 5 as distinction between few tiny poorly formed glands versus cords and nests of malignant cells were particularly challenging. As a result, sheets of cells with ill-defined lumina were inappropriately given as Gleason pattern 5 instead of pattern 4. These discrepancies suggest that misperceptions among each Gleason pattern in the scheme exist, especially for "borderline" cases, which exhibit features intermediate between 2 patterns. In another study by Coard,[3] the greatest discordance is seen in distinguishing Gleason score 6 from 7 in biopsy specimens with less than 30% tumor volume. This has led to the conclusion that assignment of Gleason scores in core needle samples, in contrast to TURP and radical prostatectomy specimens, poses a diagnostic dilemma as these samples contain low tumor volume.[4,5] Several data support that for needle biopsy grading, pathologist training and experience can influence the degree of interobserver agreement.[6,7] In one study,[7] 41 general pathologists exhibited moderate interobserver agreement with a kappa coefficient of 0.435, while substantial interobserver agreement with a kappa coefficient of 0.6-0.7 was seen among 9 of 10 urologic pathologists. Interest in urologic pathology, particularly in Gleason scoring, resulted in participation of general pathologists in educational courses and subspecialty training, which however is not readily available in our setting. Other sources of grading variation in core needle samples include difficulty in appreciation of infiltrative growth pattern, tissue sampling error and artifactual tissue distortion.

A structured histopathology report for prostate needle biopsies has an essential role in conveying the result to clinicians. The report should be uniform and formatted to provide compete, clear and unambiguous data. The inclusion of tumor volume and presence of extraprostatic extension, perineural and lymphovascular invasion, prostatic intra-epithelial neoplasia and intraductal carcinoma in prostate needle biopsy reports are equally essential as the Gleason score, and must be reported when present since these are associated with adverse clinical outcome.[8] Moreover, these pathologic findings are being utilized in common nomograms used to guide clinical decision making and therefore must be reported when present. In one study by Kryvenko et al.,[1] analysis of needle biopsy cores showed that the number of positive cores, tumor volume and perineural invasion predicts presence of extraprostatic extension, seminal vesicle invasion and positive surgical margins in radical prostatectomy specimens. In the same study, they concluded that biopsy specimens with perineural invasion is significantly associated biochemical recurrence.

With these in mind, our study intends to 1) determine the interobserver agreement of the respondent pathologists in Gleason grading of prostatic adenocarcinoma in terms of: primary grade, secondary grade, Gleason score and Gleason Grade Group; and 2) describe the completeness of reporting of histopathology results by respondent pathologists in terms of inclusion of tumor volume and mention of presence of extraprostatic extension, perineural and lymphovascular invasion, prostatic intra-epithelial neoplasia and intraductal carcinoma.

METHODOLOGY

Board certified fellows or diplomates in anatomic pathology by the Philippine Society of Pathologists who acquired no formal training in uropathology and practicing as a general pathologist were recruited for this study. Information on respondents' age, number of years in practice, current affiliation/s and other demographic profiles were not collected. They were invited to take part in the study via phone calls, letters and emails. Our study welcomed 18 pathologists from all over the Philippines, including areas outside Metro Manila such as Ilocos Norte, Cagayan, Isabela, Zamboanga, Cebu and Davao. A set of 19 slides diagnosed by a uropathologist with prostatic adenocarcinoma at St. Luke's Medical Center Quezon City was sent to the respondent pathologists. These cases were seen by a second pathologist from the same institution who concurred with the diagnosis. The slides were selected by the original sign-out pathologist to roughly represent the spectrum of Gleason scores based on the 2015 Modified Gleason Grading System and no effort was made to select particularly difficult cases. The slides, in hematoxylin and eosin preparation, was of uniform and adequate quality and was assessed prior to shipping to ensure proper and easeful examination. Also sent along with the slides was a copy of the questionnaire and endorsement letter.

The questionnaire had assigned codes (P1-P18) to maintain the respondent's anonymity while the endorsement letter contained a brief description of the study. Each slide was given a code number (1-19) to maintain patient's anonymity and to ensure that these could not be identified by the respondent pathologists. Each respondent was instructed to give a complete diagnosis as they normally would with their own cases. He/she reviewed the slides without the knowledge of the previous Gleason scores. The interobserver agreement was evaluated using Spearman's rank correlation coefficient. Agreement was calculated for primary grade, secondary grade, Gleason score and Gleason grade group (based on 2015 ISUP and 2016 WHO grading system). The completeness of reporting of each pathologist was evaluated by the mention or failure to mention of tumor volume, extraprostatic extension, perineural and lymphovascular invasion, prostatic intra-epithelial neoplasia and intraductal carcinoma. Institutional Review and Ethics Research Committee approval was secured prior to the commencement of this study.

RESULTS

To assess for interobserver agreement, a mathematical consensus was first calculated (Table 1). The overall percentage of Gleason score agreement for all respondents is 43.0% (10.5% to 68.4%) (Table 2). The maximum number of readings were in the Gleason score 7 (33.9%; n=78/342) and least in Gleason score 2-4 (3.2%; n=11/342).

The distribution of percentage agreement for Gleason score with consensus score was computed (Table 3). 43% (n=147/342) of all assigned Gleason scores were in exact agreement with the consensus score. 72.8% and 83.6% of the assigned Gleason score were within ±1 and ±2 of the consensus score, respectively. Agreement was best in Gleason 9 (75%; n=25/33) and worst with Gleason 3 (0%; n=0/18) and Gleason 8 (30%; n=30/100). Overall, undergrading was seen in 30.4% while overgrading was seen in 26.9% of the readings. Most commonly undergraded is Gleason score 8 (46/100; 46%) while Gleason score 6 is most commonly overgraded (43/114; 38%).

Interobserver Spearman's rank correlation coefficient for primary grade, secondary grade Gleason score and Gleason grade group were computed (Table 4). Majority had moderate to low correlation (64.7%; n=198/306) in the primary grade while majority had negligible correlation (61.4%; n=188/306) for secondary grade. Likewise, moderate correlation (35.9%; n=110/306) was seen in the majority of the Gleason scores and moderate correlation (39.2%; n=120/306) with the Gleason grade group.

A total of 8 respondents (44.4%; n=8/18) mentioned at least 1 other histopathologic finding (Table 5).

Table 1. Mathematical consensus score per slide

	Median of primary score	Median of secondary score	Mathematical consensus score
Slide 1	3	3.5	7
Slide 2	3	3	6
Slide 3	3	3	6
Slide 4	3	3	6
Slide 5	4	4	8
Slide 6	2	1	3
Slide 7	3	4	7
Slide 8	4	4	8
Slide 9	3	4	7
Slide 10	3	3	6
Slide 11	4	4	8
Slide 12	3	3	6
Slide 13	5	4	9
Slide 14	4	4	8
Slide 15	4	4	8
Slide 16	3	3	6
Slide 17	5	4	9
Slide 18	4	4	8
Slide 19	4	3	7

DISCUSSION

Agreement was best seen in Gleason score 9. This is may be due to the straightforward identification of sheets, cords and solid nests of infiltrative neoplastic cells and necrosis and the large tumor volume of such poorly differentiated neoplasms.

Table 2. Percent agreement with Gleason score

Respondents	Gleason scores					Total number of readings	Percent agreement with consensus
	0-1	2-4	5-6	7	8-10		
1	0	0	3	9	7	19	47.4
2	0	0	6	7	6	19	57.9
3	0	4	4	8	3	19	21.1
4	3	1	9	6	0	19	26.3
5	0	0	1	9	9	19	36.8
6	3	0	4	8	4	19	47.4
7	2	0	4	2	11	19	47.4
8	0	0	3	4	12	19	36.8
9	0	0	0	13	6	19	47.4
10	2	0	6	5	6	19	68.4
11	4	0	8	3	4	19	31.6
12	3	0	0	5	11	19	36.8
13	3	0	0	7	9	19	42.1
14	1	0	4	6	8	19	52.6
15	1	0	4	6	8	19	52.6
16	2	0	7	7	3	19	52.6
17	0	6	9	3	1	19	10.5
18	1	0	6	8	4	19	57.9
Total	25	11	78	116	112	342	43.0

Table 3. Distribution of percentage of agreement of Gleason scores

Consensus Gleason score	Number of reading with							Total number of reading
	<-3	-2	-1	Exact	+1	+2	>+3	
3	9	0	0	0	0	0	9	18
6	17	2	4	48	28	10	5	114
7	6	3	8	44	8	4	4	77
8	4	6	36	30	16	8	0	100
9	2	4	2	25	0	0	0	33
Total	38	15	50	147	52	22	18	342
Percentage	11.1	4.4	14.6	43	15.2	6.4	5.3	

Table 4. Spearman's rank correlation coefficient for primary score, secondary score, Gleason score and Gleason grade group

Correlation	Value	Primary Grade		Secondary grade		Gleason score		Gleason grade group	
		Number of readings	%	Number of readings	%	Number of readings	%	Number of readings	%
Very high	0.9-1.00	2	0.7	2	0.7	4	1.3	6	2
High	0.7-0.89	30	9.8	4	1.3	26	8.5	42	13.7
Moderate	0.5-0.69	96	31.4	28	9.2	110	35.9	120	39.2
Low	0.3-0.49	102	33.3	84	27.5	96	31.4	86	28.1
Negligible	0.0-0.29	76	24.8	188	61.4	70	22.9	52	17
		306	100	306	100	306	100	306	100

Table 5. Mention or failure to mention of other pertinent histopathologic findings*

Respondent	Mention of other histopathologic findings*
1	Mention
2	No mention
3	No mention
4	No mention
5	No mention
6	Mention
7	Mention
8	Mention
9	Mention
10	No mention
11	Mention
12	No mention
13	No mention
14	No mention
15	No mention
16	Mention
17	No mention
18	Mention
Total	8 (n=8/18; 44.4%)

* Tumor volume, extraprostatic extension, perineural and lymphovascular invasion, prostatic intra-epithelial neoplasia and/or intraductal carcinoma

Predictably, underscoring is seen more often than overscoring. Literature has supported the fact that there is a natural tendency to underscore in such small specimens, most especially for low tumor volume cores and is may be due to the difficulty in appreciating the infiltrative nature of the tumor.

In contrast, overscoring of consensus score 7 was seen and is may be due to the challenging distinction between subtle differences in poorly formed glands and well-formed glands and/or the loss of acinar spaces caused by compression artifact. There is moderate to low correlation between the primary grades and negligible correlation between the secondary grades. This is because of the problems faced in determining the predominant pattern present in one core.

The presence of 2 distinct patterns in seemingly equal proportions and/or the discontinuous arrangement of neoplastic cells complicate the assignment of a primary grade. The most striking observation for consensus score, however, is the presence of Gleason score <6, which is traditionally not assigned to needle biopsy specimens using the upgraded Gleason grading system. This ascertains that some pathologists are indeed still using the outdated Gleason scoring system.

Majority of the histopathology reports were incomplete. This indicates that a non-standardized histopathology report is still currently being used which makes interpretation of report between institutions challenging.

CONCLUSION

Overall, tumor heterogeneity giving rise to various patterns/mimickers and the presence of morphologically borderline tumors complicates Gleason scoring. We strongly believe that subjectivity will always be present in any grading system and that a good agreement can only achieved by understanding the definition of each pattern in the scheme, as well as the pitfalls, in the updated Gleason grading system. In addition, our study puts emphasis that a complete histopathologic report is an important contributor to the success of patient management. The need to identify relevant histopathologic findings, which are often, overlooked greatly impact patient management.

ACKNOWLEDGMENTS

The authors extend their gratitude to the consultants of St. Luke's Medical Center Quezon City Institute of Pathology, all the respondent pathologists of this study for sharing their knowledge, and to the staff of the Histopathology Section of St. Luke's Medical Center Quezon City for their kind assistance during the collection of test materials.

STATEMENT OF AUTHORSHIP

All authors certified fulfillment of ICMJE authorship criteria.

AUTHOR DISCLOSURE

The authors declared no conflict of interest.

FUNDING SOURCE

None.

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OPEN ACCESS – ORIGINAL ARTICLE

Commercially Bottled Purified Water as an Alternative Instrument Feed Water in Automated Time-Resolved Fluorescent Immunoassay for TSH, 17-OHP and IRT in Neonatal Screening

Emilio Villanueva III,[1,2] Roel Martin. Bumalay,[1] John Michael Rivera[1]

[1]*Newborn Screening Center – Southern Luzon*
[2]*Department of Pathology, University of the Philippines–College of Medicine*

ABSTRACT

Objective. The study was undertaken to determine if commercially bottled purified water can be used as substitute instrument feed water for three (3) newborn screening immunoassays.

Methodology. A total of 294 control samples and 300 patient samples were included in this study. Accuracy and precision studies using control samples, and parallel testing using patient samples, were done to compare the use of clinical laboratory reagent water (CLRW) and commercially bottled purified water (CBPW) in the performance of automated time-resolved fluorescent immunoassay of thyroid stimulating hormone (TSH), 17a-OH-progesterone (17-OHP) and immunoreactive trypsinogen (IRT).

Results. The use of CBPW as instrument feed water for measurements of TSH, 17-OHP and IRT levels by automated time-resolved fluorescent immunoassay using AutoDELFIA (Perkin-Elmer) in NBS has an acceptable accuracy and precision compared to using CLRW. The parallel testing using patient samples showed that, overall, the performance of using CBPW in automated time-resolved fluorescent immunoassay for TSH, 17-OHP, and IRT is acceptable, compared with using CLRW as instrument feed water.

Conclusion. Commercially bottled purified water can be used as substitute when setting up a laboratory water purification system is too expensive for a laboratory, or as back up to clinical laboratory reagent water when there is breakdown of the installed water purification system to be used as instrument feed water in automated time-resolved fluorescent immunoassay of TSH, 17-OHP and IRT in NBS using AutoDELFIA (Perkin-Elmer).

Key words: fluorescent antibody technique, immunoassay, neonatal screening, clinical laboratory reagent water

ISSN 2507-8364 (Online)
Printed in the Philippines.

Received: 3 October 2018.
Accepted: 5 November 2018.
Published online first: 5 November 2018.
https://doi.org/10.21141/PJP.2018.011

Corresponding author: Emilio Q. Villanueva III, MD, DPSP
E-mail: eqvillanueva@up.edu.ph

INTRODUCTION

The Newborn Screening Study Group (NSSG) first conceptualized newborn screening (NBS) in the Philippines in 1996. The initial objectives of the Philippine Newborn Screening Project (PNBSP) were to establish the incidence data of six metabolic conditions – congenital hypothyroidism (CH), congenital adrenal hyperplasia (CAH), galactosemia (GAL), phenylketonuria (PKU), homocystinuria (HCY), and glucose-6-phosphate dehydrogenase (G6PD) deficiency, and to make recommendations for the adoption of newborn screening nationwide.[1] This project has been successful as a newborn screening bill was introduced and was signed into law in 2004 as Republic Act 9288 or Newborn Screening Act of 2004. This law requires that every newborn must be given access to NBS by the attending or assisting health practitioner.[2] Later on, there was discontinuation of screening for homocystinuria as a cost-cutting measure due to non-detection of cases, and inclusion of screening for maple syrup urine disease (MSUD) as part of the six basic screened disorders. Additional disorders were included in the expanded NBS (eNBS) in 2014. It included screening for cystic fibrosis (CF), biotinidase deficiency (BTND), hemoglobinopathies (HBP), amino acid

metabolism disorders (AAD), acylcarnitine metabolism disorders (ACD), fatty acid oxidation disorders (FAO), and urea cycle disorders (UCD).

NBS for primary CH is done through determining the TSH level on a dried blood spot (DBS).[3] Infants with significantly elevated DBS TSH indicate risk for primary CH. An elevated serum TSH and a low serum FT4 confirm primary CH.[4] The 17α-OH-progesterone (17-OHP), a precursor of cortisol, is increased in the 2 most common types of CAH, i.e., 21- and 11β-hydroxylase deficiencies. Therefore, measuring the 17-OHP levels on DBS is a useful NBS method for the detection of CAH.[5] Infants with moderate to severe elevation of 17-OHP, and those who have mild elevation of 17-OHP and are low birth weight must undergo confirmatory tests with plasma 17-OHP, sodium, potassium, cortisol and glucose.[4] Screening for CF entails for initial measurement of IRT levels on DBS. An elevated IRT level signifies an increased risk of CF. The neonate then undergoes confirmatory testing wither by sweat test for chloride or a DNA test for CFTR mutations.[6] Since the initiation of the NBS in the Philippines, fluorescent immunoassay is the recommended laboratory method for NBS of CH, CAH, and CF.[1,7-9]

Automated methods for detecting TSH and 17-OHP use solid phase time-resolved fluorescent immunoassay. Solid-phase methods utilize a washing step to separate the bound analyte, which is immobilized by the antibody attached to a solid support, from the unbound, which is washed away.[10] The presence of analyte is then detected by labeled indicator reagents using different techniques.[11] The TSH and IRT assays are based on a direct sandwich technique where two monoclonal antibodies recognize separate antigenic determinants on the TSH molecule. The fluorescence signal is proportional to the TSH concentration in the sample.[12] The 17-OHP assay, on the other hand, is based on the competitive binding of Europium-labeled 17-OHP, and 17-OHP in the sample to 17-OHP-specific antibodies. The fluorescence signal is inversely proportional to the 17-OHP concentration in the sample.[13] Excess, unbound labeled indicator reagents will be washed by another washing step before instrument reading.

Clinical laboratory reagent water (CLRW) should be pure enough to satisfy the requirements of most clinical laboratory testing. CLRW must have resistivity ≥ 10 MΩ.cm referenced to 25°C, total heterotrophic plate count <10 CFU/mL, total organic carbon <500 ng/g, and particulate content sizes of <0.22 μm. The CLRW are prepared though different available laboratory water purification systems. The automated method for time-resolved fluorescent immunoassay utilizes this CLRW as instrument feed water for internal washing, rinsing and dilution.

Commercially bottled purified water (CBPW) refers to water that is marketed for drinking.[14] Manufacture of CBPWs is regulated by law and should follow standards prior to commercial release for consumption. The Department of Health Administrative Order 10 series of 2017 requires the following physico-chemical and microbiologic standards: CBPW must have resistivity ≥0.2 MΩ.cm referenced to 25°C, total heterotrophic plate count <500 CFU/mL, and organic chemicals <0.0002 to 1mg/L, depending on the particular organic chemicals. There is no specified standard for total organic carbon and particulate content sizes.[15]

The objective of this study is to determine if CBPW, particularly Wilkins distilled water, can be used as substitute when setting up a laboratory water purification system is too expensive for a laboratory, or as back up to CLRW when there is breakdown of water purification systems, in the performance of automated time-resolved fluorescent immunoassay of TSH, 17-OHP, and IRT using AutoDELFIA (Perkin-Elmer) for NBS.

The study is limited to the evaluation of the above-mentioned analytes. These are the only analytes measured by automated time-resolved fluorescent immunoassay using AutoDELFIA (Perkin-Elmer) in NBS in the Philippines.

METHODOLOGY

A total of 294 control samples and 300 patient samples were included in this study. There were 61 low and 61 high TSH controls, 55 low and 55 high 17-OHP controls, 31 low and 31 high IRT controls, 100 TSH patient samples, 100 17-OHP patient samples, and 100 IRT patient samples. A single analyst did the sample preparation and operation of the instrument to control for possible inter-analyst variability in technique. A single reagent kit lot was used to control for possible inter-lot variability in the chemical reactions. Finally, a single automated time-resolved fluorescent immunoassay instrument using AutoDELFIA (Perkin-Elmer) was used to control for possible inter-machine variability in instrument performance. The type of water used, i.e. CLRW or CBPW (using Wilkins distilled water), was the experimental intervention for this study.

There were two phases of the study; first is the accuracy and precision studies. The accuracy of using CBPW in measuring control samples was compared to the reference method, i.e., using CLRW as instrument feed water. Mean and deviation were the statistic used to evaluate accuracy. A deviation less than |10%| and/or t-test between two independent means with $t < Critical_t$ indicates an acceptable accuracy. The precision of CBPW compared to the precision of the CLRW in measuring control samples. Standard deviation (SD) and Coefficient of variation (CV) were the statistic used to evaluate accuracy. A CV less than |10%| and/or F-test between two variances with $F < Critical_F$ indicates an acceptable precision.

The second part of the study is the parallel testing using patient samples. Bland-Altman analysis, Passing Bablok regression, and *kappa* statistic are used to evaluate the performance of using CBPW compared to using CLRW as instrument feed water. A bias less than |10%|, slope of between 0.90 to 1.10, linearity of 0.975 to 1.000, and *kappa* greater than 0.90 indicates an acceptable comparable performance of using CBPW in automated time-resolved fluorescent immunoassay.

Table 1. Evaluation of accuracy and precision of CBPW in comparison to CLRW as instrument feed water for measurements of the 17-OHP, TSH, and IRT levels by automated time-resolved fluorescent immunoassay using AutoDELFIA (Perkin-Elmer) in NBS

	Statistic	CLRW	CBPW	CLRW	CBPW
Control Level		*Low*		*High*	
17-OHP	Count	29	32	29	32
Accuracy	Mean	65.72	64.66	147.88	145.59
	Deviation	1.62%		1.55%	
	t	0.8258		0.6156	
	Critical value t	2.0010		2.0010	
Precision	SD	5.67	4.32	14.95	14.10
	CV	8.63%	6.69%	10.11%	9.68%
	F	1.7227		1.1242	
	Critical value F	1.8303		1.8303	
TSH	Count	24	31	24	31
Accuracy	Mean	14.77	14.28	57.96	57.21
	Deviation	3.32%		1.29%	
	t	1.4967		0.5551	
	Critical value t	2.0057		2.0057	
Precision	SD	1.05	1.31	5.23	4.76
	CV	7.07%	9.19%	9.02%	8.33%
	F	1.5566		1.2072	
	Critical value F	1.9605		1.8972	
IRT	Count	15	16	15	16
Accuracy	Mean	58.26	60.08	91.48	94.96
	Deviation	-3.12%		-3.80%	
	t	-1.7439		-1.654	
	Critical value t	2.0452		2.0452	
Precision	SD	2.69	3.09	5.18	6.42
	CV	4.62%	5.14%	5.66%	6.76%
	F	1.3195		1.5361	
	Critical value F	2.4630		2.4630	

RESULTS

Accuracy and Precision Studies

A total of 294 control samples were included in this phase. The results are summarized in Table 1. There were no significant mean differences in the measurements of the 17-OHP, TSH, and IRT levels of low and high control samples between CLRW and CBPW ($t < Critical_t$). The percent deviations of CBPW from CLRW were less than |10%| for all analytes and control levels. There was no significant difference in variances in the measurements of the 17-OHP, TSH, and IRT levels of low and high control samples between CLRW and CBPW ($F < Critical_F$), and the CV of CBPW were less than |10%| for all analytes and control levels. This indicates that using CBPW as instrument feed water for measurements of the 17-OHP, TSH, and IRT levels by automated time-resolved fluorescent immunoassay using AutoDELFIA (Perkin-Elmer) in NBS has an acceptable accuracy and precision.

Parallel Testing of Patient Samples

A total of 300 patient samples were included in this phase. The results of Bland-Altman analysis and Passing Bablok regression analysis are summarized in Table 2. Generally, CBPW gives higher results than CLRW, with % bias less than |10%| for all analytes, and the slope and linearity are within 0.90 to 1.10 and 0.975 to 1.000, respectively.

Evaluation of the Bland-Altman plot and Passing Bablok regression line (Figures 1-6) shows that values near the cut-off values for 17-OHP, TSH, and IRT are within the agreement limits, and are close to the best fitted line, respectively. This may indicate that using CBPW as an alternative to CLRW would not misclassify the result of the screening test.

Table 2. Parallel testing of CBPW and CLRW as instrument feed water for measurements of the 17-OHP, TSH, and IRT levels by automated time-resolved fluorescent immunoassay using AutoDELFIA (Perkin-Elmer) in NBS

Statistic	17-OHP	TSH	IRT
Count	100	100	100
Bias	3.43%	8.73%	9.04%
Slope	0.9989	1.0481	1.0819
Linearity	0.9966	0.9983	0.9973

In NBS, it is the delineation of a positive versus a negative screen which is more critical than the actual quantitative value; therefore, the agreement in terms of *kappa* of the screening status of both methods is more significant to evaluate. Based on *kappa* statistic, there is a perfect level of agreement in the identification of positive screen between CBPW and CLRW (Tables 3-5).

The parallel testing showed that overall, the performance of using CBPW in automated time-resolved fluorescent immunoassay for TSH, 17-OHP, and IRT is acceptable, compared with using CLRW as instrument feed water.

DISCUSSION

Time-resolved fluorescent immunoassay is widely used for measurement of various hormones in biological specimens.[16] As a solid-phase method, a washing step is needed in order to remove unbound analytes, and unbound labeled indicator reagents that may create background noise to the signal detected by the instrument.[17] CLRW are used as instrument feed water in automated instruments for this purpose.[14]

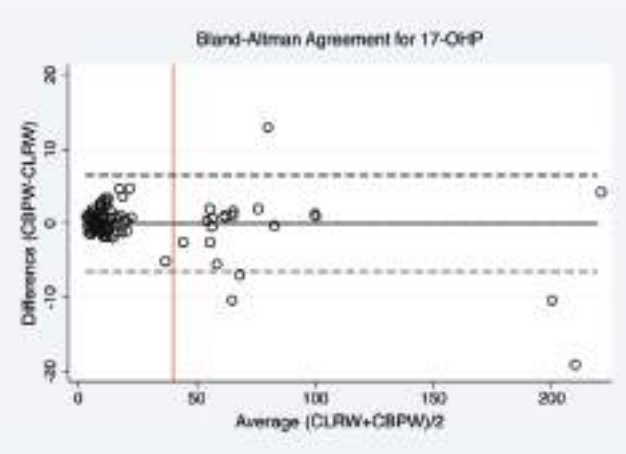

Figure 1. Bland-Altman plot of CBPW and CLRW as instrument feed water for measurements of the 17-OHP levels by automated time-resolved fluorescent immunoassay using AutoDELFIA (Perkin-Elmer) in NBS. *(Note: Red line indicates cut-off value).*

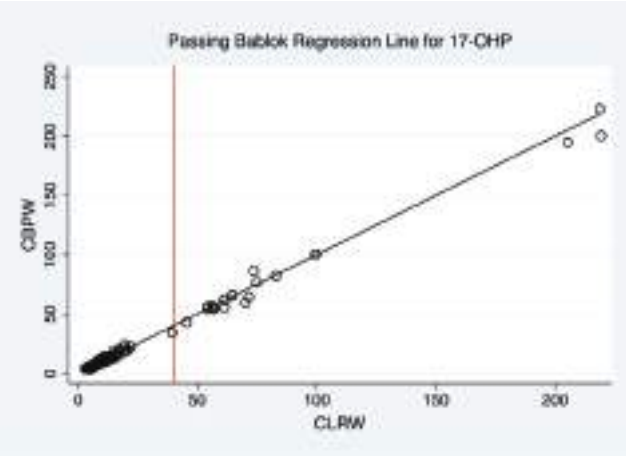

Figure 2. Passing Bablok regression line of CBPW and CLRW as instrument feed water for measurements of the 17-OHP levels by automated time-resolved fluorescent immunoassay using AutoDELFIA (Perkin-Elmer) in NBS. *(Note: Red line indicates cut-off value).*

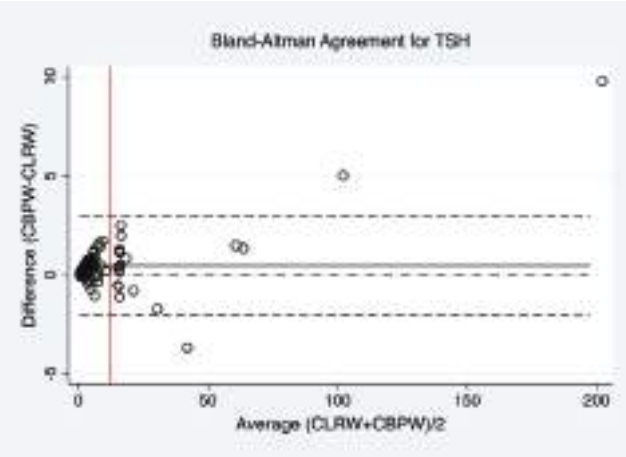

Figure 3. Bland-Altman plot of CBPW and CLRW as instrument feed water for measurements of the TSH levels by automated time-resolved fluorescent immunoassay using AutoDELFIA (Perkin-Elmer) in NBS. *(Note: Red line indicates cut-off value).*

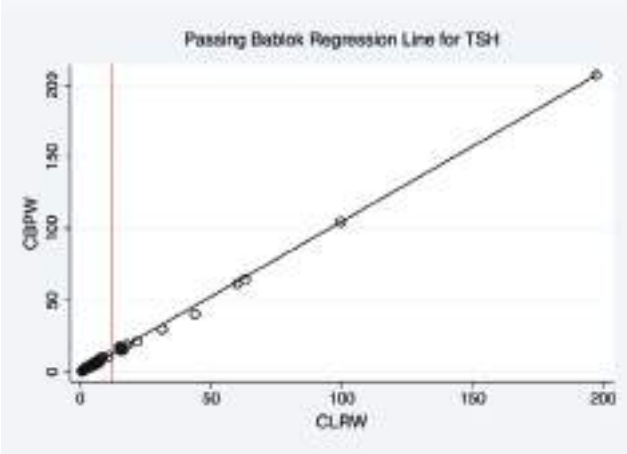

Figure 4. Passing Bablok regression line of CBPW and CLRW as instrument feed water for measurements of the TSH levels by automated time-resolved fluorescent immunoassay using AutoDELFIA (Perkin-Elmer) in NBS. *(Note: Red line indicates cut-off value).*

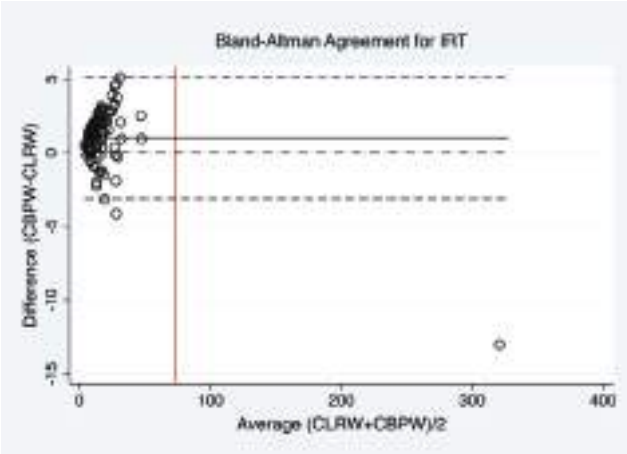

Figure 5. Bland-Altman plot of CBPW and CLRW as instrument feed water for measurements of the IRT levels by automated time-resolved fluorescent immunoassay using AutoDELFIA (Perkin-Elmer) in NBS. *(Note: Red line indicates cut-off value).*

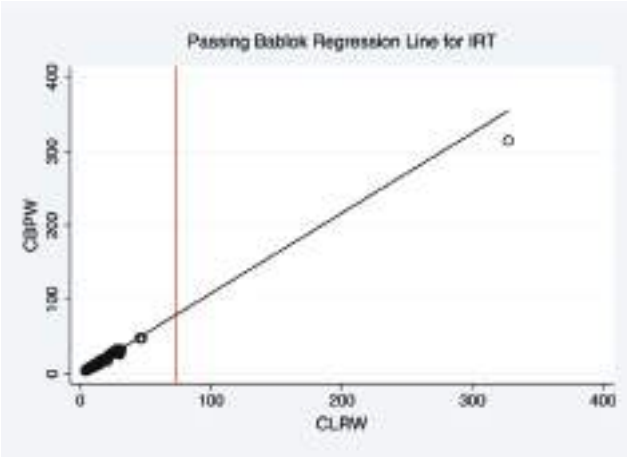

Figure 6. Passing Bablok regression line of CBPW and CLRW as instrument feed water for measurements of the IRT levels by automated time-resolved fluorescent immunoassay using AutoDELFIA (Perkin-Elmer) in NBS. *(Note: Red line indicates cut-off value).*

Table 3. 17-OHP screening agreement between CLRW and CBPW

CBPW	CLRW	
	Positive	Negative
Positive	20	0
Negative	0	80
Kappa	1	
Agreement	100%	
Expected Agreement	68.00%	

Table 4. TSH screening agreement between CLRW and CBPW

CBPW	CLRW	
	Positive	Negative
Positive	20	0
Negative	0	80
Kappa	1	
Agreement	100%	
Expected Agreement	68.00%	

Table 5. IRT screening agreement between CLRW and CBPW

CBPW	CLRW	
	Positive	Negative
Positive	1	0
Negative	0	99
Kappa	1	
Agreement	100%	
Expected Agreement	98.02%	

CBPW may have met the specifications for CLRW when it was bottled by the manufacturer, however, it is recommended that laboratories must validate that the bottled water is fit for its intended purpose in their setting.[14]

In this study, we have validated the use of CBPW, and have observed that it has no significant difference in the performance of automated time-resolved fluorescent immunoassay for TSH, 17-OHP, and IRT compared with using CLRW as instrument feed water.

CONCLUSION

Based on our findings, we conclude that CBPW can be used as substitute to CLRW as instrument feed water in automated time-resolved fluorescent immunoassay of TSH, 17-OHP, and IRT in NBS using AutoDELFIA (Perkin-Elmer).

STATEMENT OF AUTHORSHIP

All authors certified fulfillment of ICMJE authorship criteria.

AUTHOR DISCLOSURE

The authors declared no conflict of interest.

FUNDING SOURCE

None.

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External Quality Assessment Scheme for Transfusion Transmissible Infections among Blood Service Facilities in the Philippines, 2017

Kenneth Aristotle Punzalan, Rhoda Yu, Iza Mae Chamen

Research Institute for Tropical Medicine-Department of Health, Philippines

ABSTRACT

The External Quality Assessment Scheme (EQAS) evaluates the performance of participating laboratories through an external agency by which known blinded samples are sent to participants for analysis, and their performance evaluated and monitored.

The Transfusion Transmissible Infections – National Reference Laboratory provides an external quality assessment scheme for transfusion transmissible infections to blood service facilities in the Philippines with the aim of raising the standards of quality testing in infectious diseases in blood units and as a mandatory requirement in the licensing of laboratories.

In the 2017 test event, 180 participants were given an EQAS panel composed of the HVHT4120 serology program and the MLRA415 malaria program. Results were submitted through an online informatics system managed by OneWorld Accuracy Canada using the ISO 13528:2008 Robust Statistics method (Huber's Method). Results were analyzed and evaluated with the reference result of the NRL to which non-concordant results would be marked aberrant.

From the 14,392 generated results from the HVHT4120 program and 885 generated results from the MLRA415 program, 51 (0.35%) results and 86 (9.72%) results were reported as aberrant respectively. The aberrant results reported were either due to random or systematic errors.

Analyzed data from this test event are used for the continuous improvement of their competencies and the renewal of their license to operate as required by the Department of Health.

Key words: quality assurance, blood donor serology, transfusion transmissible infections, proficiency testing

ISSN 2507-8364 (Online)
Printed in the Philippines.

Received: 29 June 2018.
Accepted: 2 September 2018.
Published online first: 16 September 2018.
https://doi.org/10.21141/PJP.2018.012

Corresponding author: Kenneth Aristotle P. Punzalan, RMT
E-mail: kenn.punzalan@gmail.com, tti.nrl@gmail.com
ORCID: https://orcid.org/0000-0002-0564-2331

INTRODUCTION

The quality management system model developed by the Clinical and Laboratory Standards Institute (CLSI), lists assessment an important element of the 12 quality system essentials and defines it as a tool for examining laboratory performance and comparing it to standards, benchmarks or the performance of other laboratories.[1] An external quality assessment scheme (EQAS) is a method by which an independent external agency uses known samples with undisclosed results and is commonly used to establish inter-laboratory comparability.[2]

In the Philippines, participation in an external quality assessment scheme for transfusion transmissible infections is a mandatory requirement for the licensure of blood service facilities[3] and aims to raise the standards on the quality testing of blood units.

This activity evaluated the performance of the blood service facilities in the Philippines by analyzing the results of the external quality assessment scheme conducted by the Transfusion Transmissible Infections – National Reference Laboratory in 2017.

METHODOLOGY

Panel Composition

The TTI EQAS 2017 test event consisted of two panels, the HVHT4120 for blood donor serology, and the MLRA415 for malaria slide microscopy. The HVHT4120 consisted of twenty (20) pooled plasma samples obtained from blood donors from different regions of the country. Each pooled sample was prepared by mixing similar volumes of at least two samples that had similar antibody and antigen profiles. All samples were subjected to filtration prior to aliquoting. The samples were aliquoted, and their homogeneity confirmed. The serology profile for HIV, HBV, HCV, Syphilis of each sample were identified using a chemiluminescence assay (ChLIA), enzyme immunoassay (EIA), Rapid Plasma Reagin (RPR), Particle Agglutination (PA) and a Differentiation/Supplemental Assay (SA).

Program code MLRA415 consists of five (5) blood smears. The samples were obtained from Malaria patients in Palawan and prepared by the NRL for Malaria and other Parasites of the Research Institute for Tropical Medicine

Participants

The multimarker blood serology EQAS panel ID HVHT4120 and malaria microscopy EQAS panel ID MLRA415 were distributed to 180 participants nationwide. These participants enrolled for the EQAS 2016 test event with a corresponding registration fee to cover expenses for the test event.

Majority of the participants were private institutions (44%) followed closely by government institutions (42%) and the remainder are from the different Philippine Red Cross chapters (14%). Figure 1 shows the distribution of participants by region.

Data Analysis

ISO 13528:2005 Robust Statistics method (Huber's Method) was used to identify outlying results (numerical test results found to be statistically different from other test results reported by participants that tested the same sample in the same assay) for the created peer groups. A peer group is defined as a set of laboratories that utilize the same test format and assay test kit for screening TTI. The said method uses the mean as an estimator and outlying test results were removed from statistical calculation. Qualitative results of the BSF were compared with the qualitative reference results of the NRL Discrepancy between the two results would mark a result aberrant.

RESULTS AND DISCUSSION

A total of 14,392 results were generated from 75 assays for the HVHT4120 panel and 885 results were generated from 1 assay for the MLRA415 panel.

Data entry errors: Two participants reported a "reactive" test result but submitted a "negative" assay interpretation.

False positive results: Nine participants reported false reactive results on known negative samples.

False negative results: Five participants reported false negative results on initial testing.

Educational sample (HIV and HCV): Two participants reported false negative results on the HIV and HCV sample with one of the participants having reported a "reactive" test result but submitted a "negative" assay interpretation. One participant had reported a reactive HBsAg result.

Educational sample (HIV p24 Antigen): Two participants reported a "reactive" result using a 3rd generation HIV assay. Eleven participants reported a "negative" result using a 4th generation HIV assay with one participant having reported a "reactive" test result but submitted a "negative" assay interpretation. Three participants reported an "inconclusive" test result using a 4th generation HIV assay. Three participants reported a reactive HBsAg result on the HIV p24 antigen sample.

Of the total number of results generated in the HVHT4120 panel, 51 results (0.35%) were reported as aberrant.

On rating the performance of the participants, the following criteria must be met to be classified as an unsatisfactory performer in the HVHT4120 initial panel:
(a) at least one false negative result;
(b) at least twenty percent (20%) false positive results.

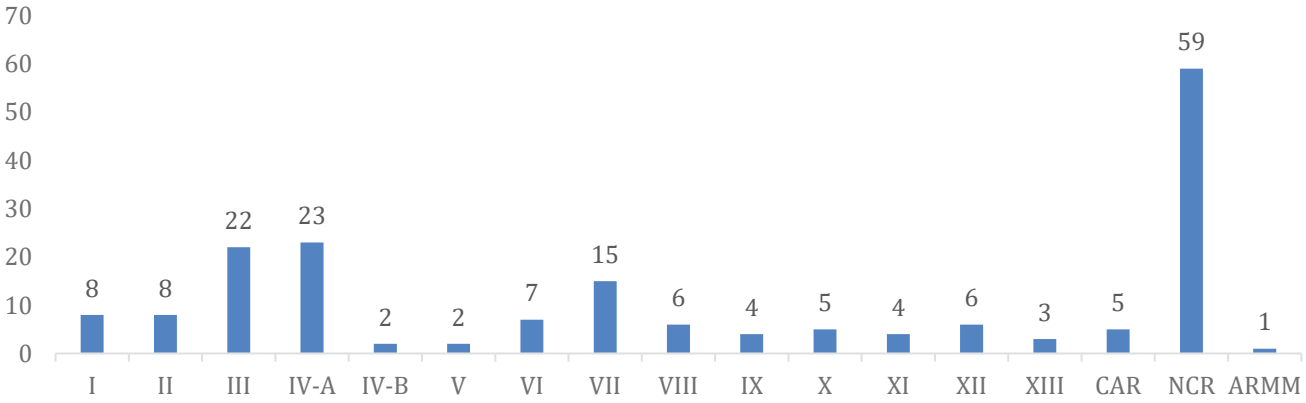

Figure 1. Regional distribution of participants.

In accordance with these criteria, corresponding participants were given an investigation checklist to assist them in identifying errors and make the necessary corrective actions and/or troubleshooting methods. A 2nd set of the HVHT4120 panel were given to participants for retesting if the identified unsatisfactory performance was due to a testing error. Participants with aberrant results due to transcription errors were only given an investigation/ troubleshooting checklist and a written recommendation. Three (10) participants were given a second set of samples wherein one participant had reported a false negative result and one participant did not submit their results.

Of the total number of results generated in the MLRA415 panel, 86 results (9.72%) were reported as aberrant.

Figure 2 shows the distribution of grades of the participants. They have been evaluated and graded as follows:

- Excellent – 100% acceptable results on the initial panel (all final results were correctly identified in comparison with the reference results);
- Very Satisfactory – Less than 100% acceptable results on the initial panel without being given a second panel for retesting.
- Satisfactory – 100% acceptable results on retesting of the second panel; or had an aberrant result in the initial panel due to a clerical error, given that the participant was able to identify this error through the EQAS investigation checklist.
- Poor – Participant did not follow minimum requirements of testing as per DOH Circular No. 2013-0132 or less than 100% acceptable results on retesting of the second panel; or had an aberrant result in the initial panel due to a clerical error which the participant had failed to identify in the EQAS investigation checklist.

CONCLUSION

EQAS is an essential element of the quality system and plays a vital role in facilitating optimal patient care.[4] The transfusion transmissible infections EQAS directed for blood service facilities was designed to assess the entire phase of testing and monitor the quality of laboratory results. This also enables the participants to compare their performance with other laboratories and this can aid them in detecting potential problems which present opportunities for improvement.

RECOMMENDATION

The participants should regularly review their results as part of quality improvement regardless of their rating. Participants should take responsibility in implementing the necessary corrective action as part of the quality assurance program in their laboratory.[5]

ACKNOWLEDGMENTS

The authors thank the TTI-NRL staff, Dr. Catherine Masangkay and Dr. Socorro Lupisan of the Research Institute for Tropical Medicine (RITM), the Health Facility Development Bureau, the Health Facility Services and Regulatory Bureau, the Department of Health – National Voluntary Blood Services Program, the National Council for Blood Services – Technical Committee, the Department of Parasitology (RITM), Philippine Red Cross – National Blood Center (Port Area), Asian Hospital and Medical Center, OneWorld Accuracy – Canada and Joe Vincini from NRL – Australia.

We would also thank all participating Blood Service Facilities for their support.

STATEMENT OF AUTHORSHIP

All authors certified fulfillment of ICMJE authorship criteria.

AUTHOR DISCLOSURE

The authors declared no conflict of interest.

FUNDING SOURCE

None.

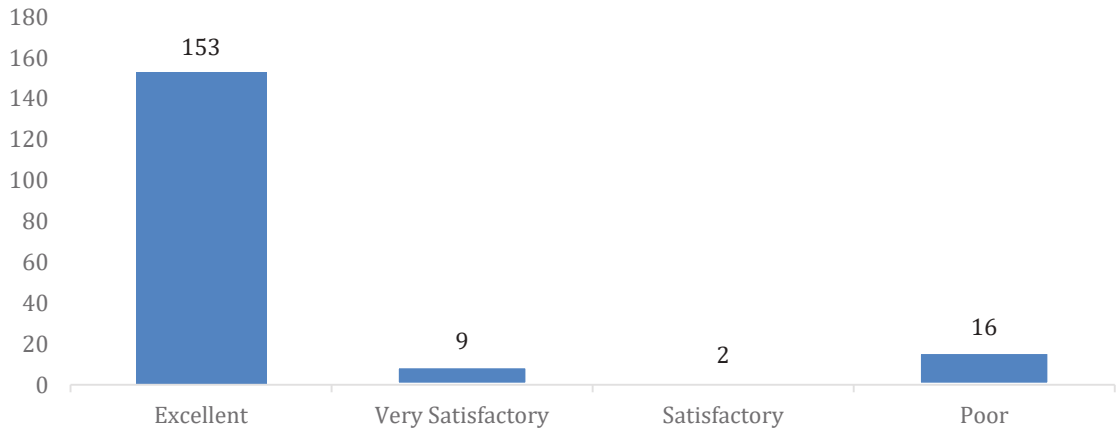

Figure 2. Distribution of grades for the EQAS 2017 test event.

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Ameloblastic Fibro-odontoma

Jay Hansel Tabije,[1] Leila Salera,[2] Jose Angelo Militante[1]

[1]*Oral and Maxillofacial Surgery and Implantology, St Jude Hospital and Medical Center, Philippines*
[2]*College of Dentistry, University of the East Manila, Philippines*

Key words: ameloblastic, fibroma, odontoma

ISSN 2507-8364 (Online)
Printed in the Philippines.

Received: 23 September 2018.
Accepted: 5 October, 2018.
Published online first: 12 October 2018.
https://doi.org/10.21141/PJP.2018.013

Corresponding author: Leila T. Salera, RN, MD, FPSP
E-mail: docleisalera@gmail.com

INTRODUCTION

A seven-year-old male was referred for consult at the oral & maxillofacial surgery & implantology section of the hospital due to a large asymptomatic left maxillary mass resulting to a noticeable facial asymmetry. Clinical examination showed a solitary bony hard swelling on the left posterior maxilla exhibiting buccal and palatal expansion. Tooth mobility of the left premolars and absent permanent molar are likewise noted (Figure 1). CT scan showed an enlarging mass on the left posterior maxilla exhibiting an amorphous ovoid opacity surrounded by a defined radiolucent border overlying the crown of a permanent molar displacing the maxillary

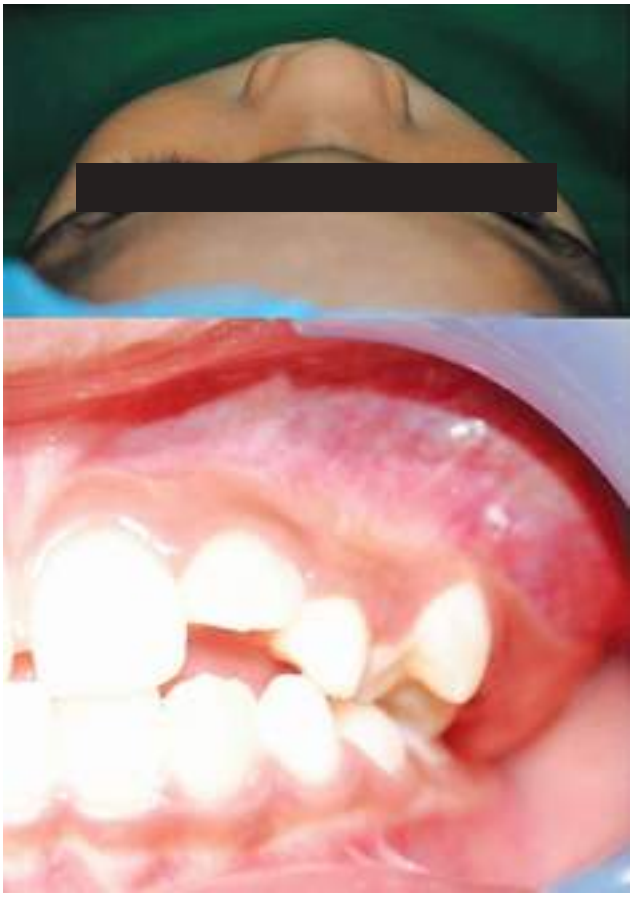

Figure 1. Clinical appearance. Mass producing facial asymmetry on left side of the patient, intra oral finding showing an evident bony hard mass on the posterior region of the left maxilla with noticeable altered eruption pattern of the left permanent molars.

sinus floor without perforating it. (Figure 2) Based on the initial diagnostics considered impressions where ameloblastic fibro-odontoma and calcifying epithelial odontogenic tumor. Patient was admitted, prepared, once cleared underwent surgical enucleation of the mass under GETA via an intra-oral Lefort 1 incision, the mass was then submitted for histopathologic examination. 11 months after the operation (Figure 3), both clinical and radiographic findings show no sign of recurrence.

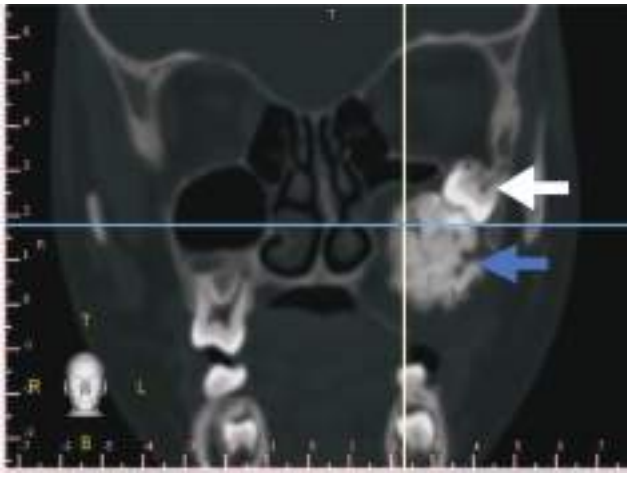

Figure 2. Coronal cut CT scan showing impacted permanent molar and large amorphous opacity surrounded by a defined radiolucency.

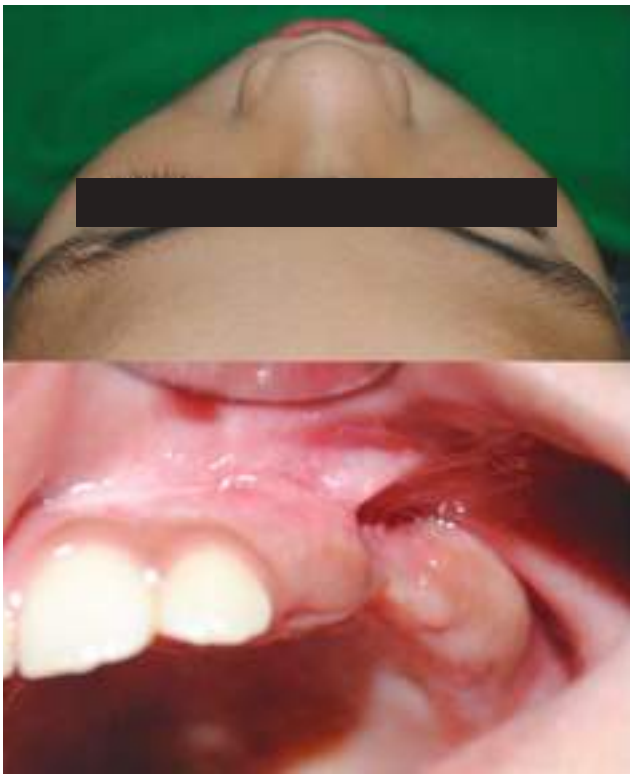

Figure 3. Clinical appearance 11 months post-operatively showing improvement in facial symmetry and defect on the operative site with no clinical sign of recurrence.

Histologic examination revealed a benign tumor composed of ameloblastic islands amidst a cellular fibrous background (Figure 4), and areas showing dentin formation. (Figure 5). Histomorphologic features were consistent with an ameloblastic fibro-odontoma.

As listed in the updated 2017 WHO classification of benign odontogenic tumors and cyst, a handful are considered calcifying types of epithelial or mixed lesions.[1] In a review by Augello et.al. regarding AFO the prevalence is set at 1-3.4% among odontogenic tumors with no gender predilection equally found on either jaw but is seen more occurring in the molar regions also associated with an impacted tooth.[2] Generally seen with a mean age of 11.5 years which together with the complaint of an asymptomatic growing mass together with the distinct calcification on diagnostic imaging can be considered an important criterion for considering AFO.[2] AFO is currently recognized as part of the histologic spectrum of developing odontomas, although it is argued that in some cases of AFO neoplastic changes may be possible specially with large AFO.[3]

AFO has histologic features identical to ameloblastic fibroma (AF) with a hard tissue component consisting of dental hard structures.[1] The AF component is the "soft tissue" component", while the "hard tissue" component contains a calcifying component composed of enamel and dentin structures.[1,4] AFO is described in its WHO (World Health Organization) classification as a lesion similar to AF, and both have been defined as hamartomatous lesions, believed to be stages of odontoma formation.[2,5] Similar to what most authors suggest this case of a large AFO was primarily managed conservatively with enucleation, reserving more ablative surgery for rare cases of recurring AFO as well as confirmed malignant transformations.

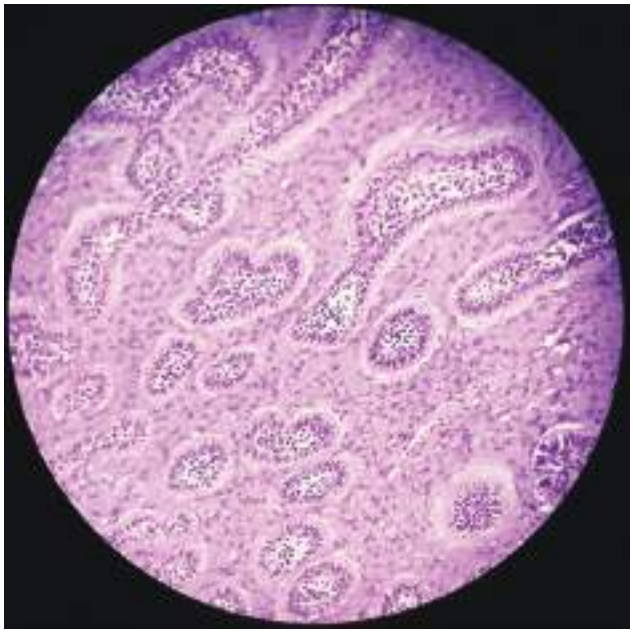

Figure 4. Ameloblastic islands in a fibromyxoid background (H & E, 40x).

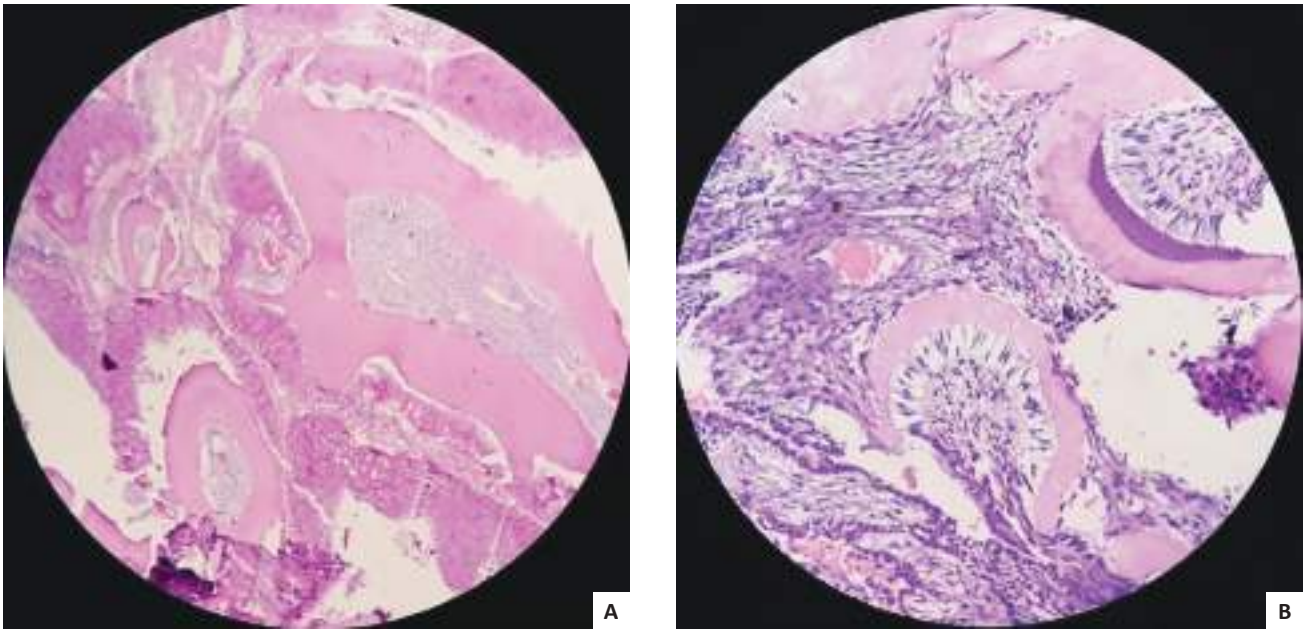

Figure 5. Areas with dentin formation (H & E, [A], 40x and [B], 100x).

ETHICAL CONSIDERATION

Patient consent was obtained before submission of the manuscript.

STATEMENT OF AUTHORSHIP

All authors certified fulfillment of ICMJE authorship criteria.

AUTHOR DISCLOSURE

The authors declared no conflict of interest.

FUNDING SOURCE

None.

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Committee on Publication Ethics (COPE), the **Directory of Open Access Journals (DOAJ),** the **Open Access Scholarly Publishers Association (OASPA),** and the **World Association of Medical Editors (WAME)** are scholarly organizations. All have seen increases in the number, and range in quality, of membership applications. Our organizations have collaborated to identify **Principles of Transparency & Best Practice for Scholarly Publications.** These principles form the basis of the criteria by which suitability for membership is assessed by **COPE, DOAJ** and **OASPA,** and part of the criteria on which membership applications are evaluated by **WAME.**

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A Journal's website, including the text that it contains, shall demonstrate that care has been taken to ensure high ethical and professional standards.

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Journal content must be clearly marked as whether peer reviewed or not. Peer review is defined as obtaining advice on individual manuscripts from reviewers expert in the field who are not part of the journal's editorial staff.

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OR

– explained to authors before they begin preparing their manuscript for submission.

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*Each organization also has their own, additional criteria which are used when evaluating applications. The organizations will not share lists of publishers or journals that failed to demonstrate that they met the criteria for transparency and best practice. This is the third version of a work in progress (published January 2018); the first version was posted on the **COPE** website on January 2014 and a second version in June 2015. We encourage its wide dissemination and continue to welcome feedback on the general principles and the specific criteria.*

publicationethics.org

doaj.org

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In the event that a member organization is found to have violated these best practices, or other specific requirements of the organization, **OASPA/DOAJ/COPE/WAME** shall in the first instance try to work with them in order to address any concerns that have been raised. In the event that the member organization is unable or unwilling to address these concerns, their membership in the organization may be suspended or terminated. All of the member organizations have procedures for dealing with concerns raised about member journals.

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Publishers and editors shall take reasonable steps to identify and prevent the publication of papers where research misconduct has occurred.

This includes but not limited to:

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In no case shall a journal or its editors encourage such misconduct, or knowingly allow such misconduct to take place. In the event that a journal's publisher or editors are made aware of any allegation of research misconduct relating to a published article in their journal, the publisher or editor shall follow **COPE's** guidelines (or equivalent).

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A journal should have policies on publishing ethics. These should be clearly visible on its website, and should refer to:

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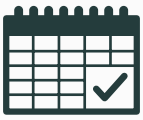
– journal's options for post-publication discussions and corrections.

PUBLISHING SCHEDULE



The periodicity at which a journal publishes shall be clearly indicated.

ACCESS

The way(s) in which the journal and individual articles are available to readers and whether there are associated subscription or pay per view fees shall be stated.

ARCHIVING

A journal's plan for electronic backup and preservation of access to the journal content shall be clearly indicated (for example, access to main articles via CLOCKSS or PubMedCentral).

This is in the event that a journal is no longer published.

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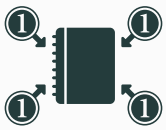

Business models or revenue sources shall be clearly stated or otherwise evident on the journal's website.

For example:

– author fees
– subscriptions
– advertising
– reprints
– institutional support
– organizational support

Publishing fees or waiver status should not influence editorial decision making.

ADVERTISING

Journals shall state their advertising policy if relevant including:

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– who makes decisions regarding accepting adverts
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DIRECT MARKETING

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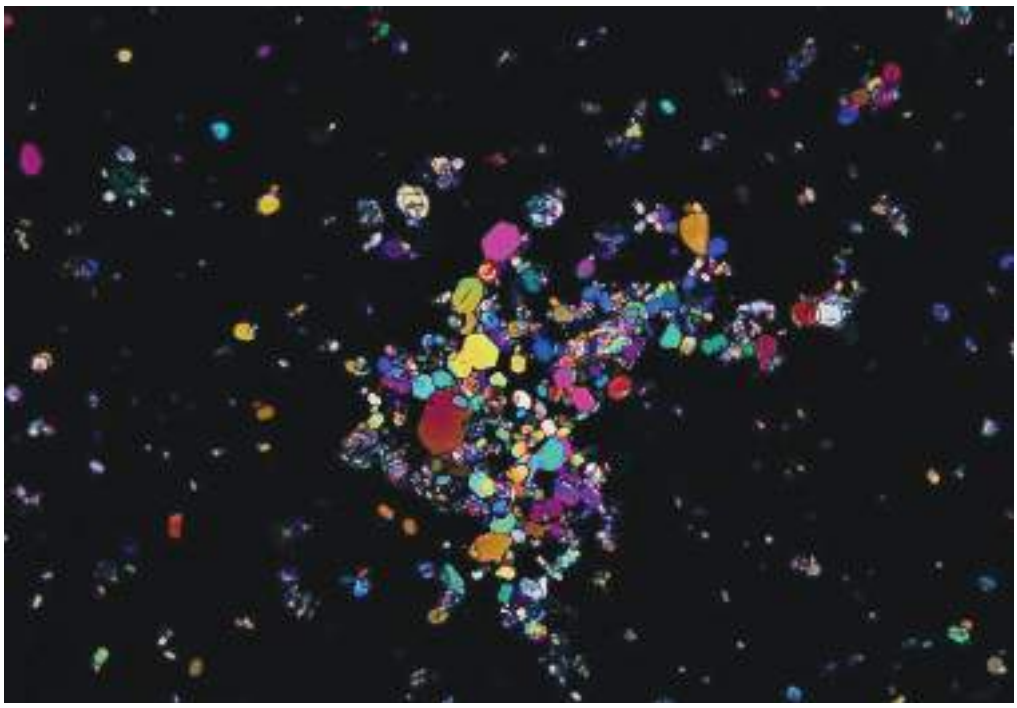
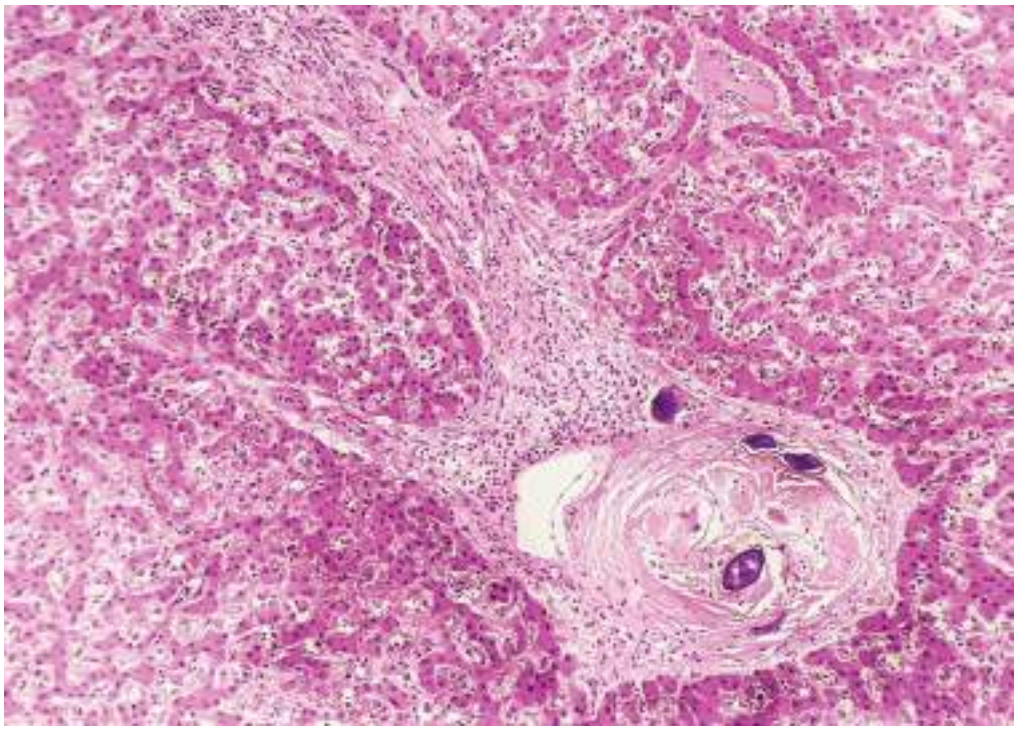
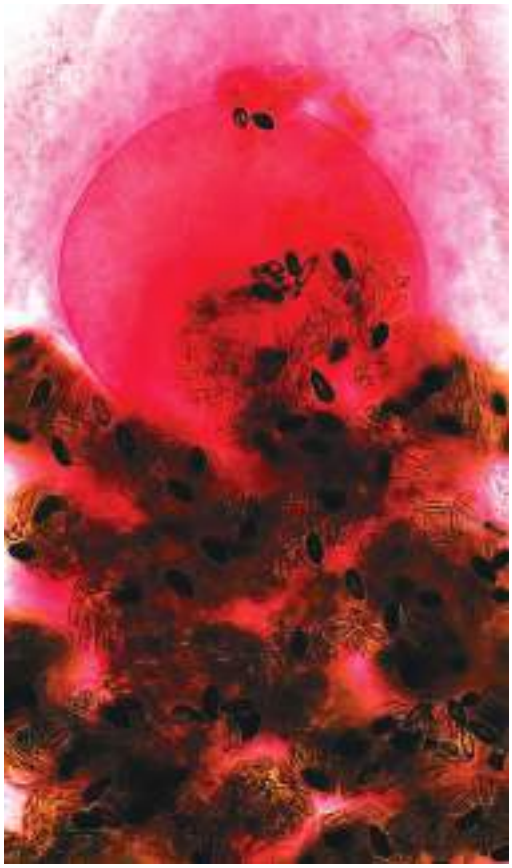


MARK JASON G. ORDENES
Urine, Total magnification used: 400x and 100x
Case of a 2-year-old male with a complaint of painful urination.

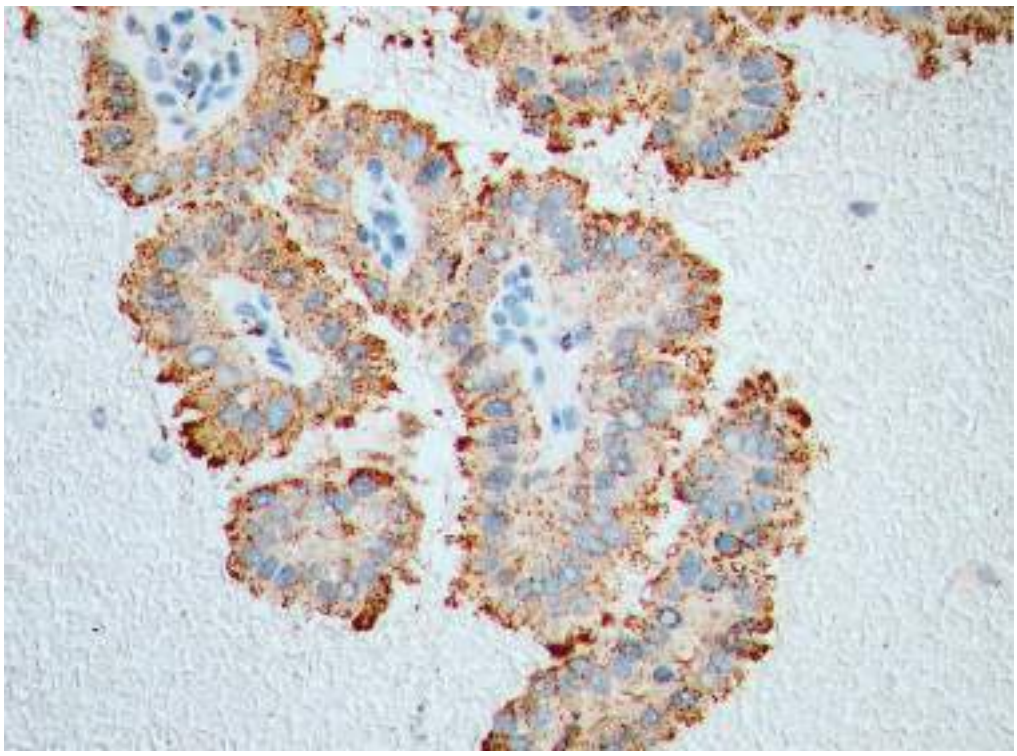


SECOND PLACE

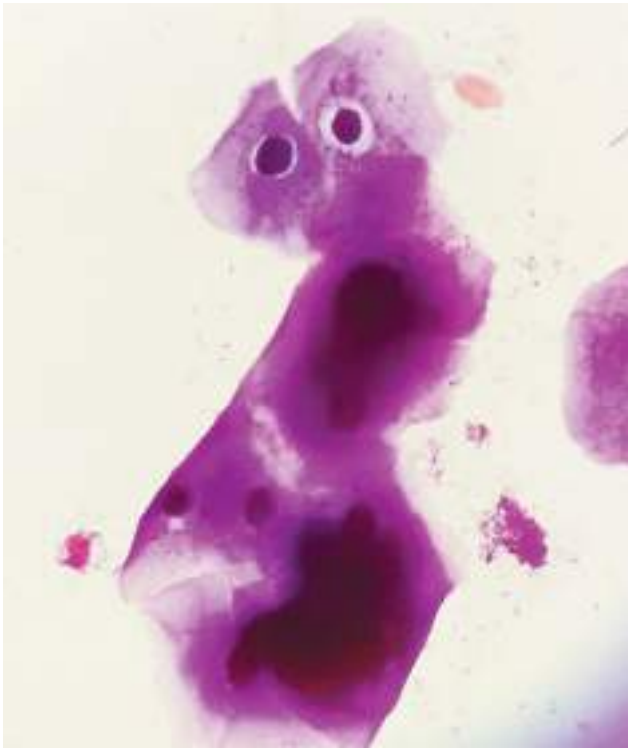
THADDEUS C. HINUNANGAN
"LAST EXIT TO LEYTE"
A 22-year-old male dies of pneumonia, but an autopsy revealed Schistosoma japonicum ova, inducing pipe stem fibrosis in the liver. The young man may have passed, but this undeniable reminder of a neglected tropical disease remains.



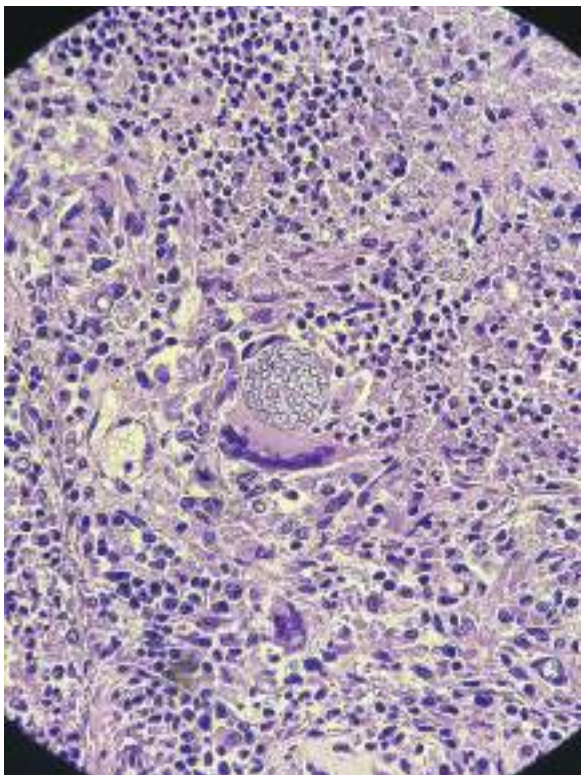
FAYE VICTORIA A. DE LOS REYES
This photomicrograph depicts the ventral sucker and part of the uterus of the Clonorchis sinensis. The numerous eggs shown is a reminder of the burden of disease in East and Southeast Asia that is caused by this organism despite being only 2.5 cm in its full adult size.



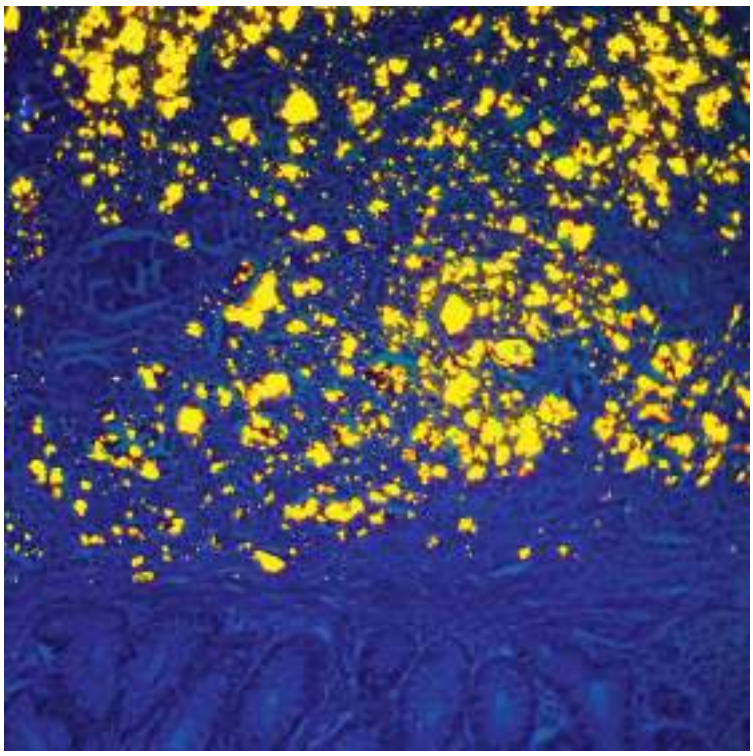
MARIA CECILIA M. DAÑGUILAN
Fine-needle aspiration biopsy of a pulmonary mass showed papillae lined by columnar cells with nuclear grooves and pseudoinclusions resembling papillary thyroid carcinoma. Granular cytoplasmic staining with Napsin A is seen in tumor cells exhibiting prominent nuclear pseudoinclusions.



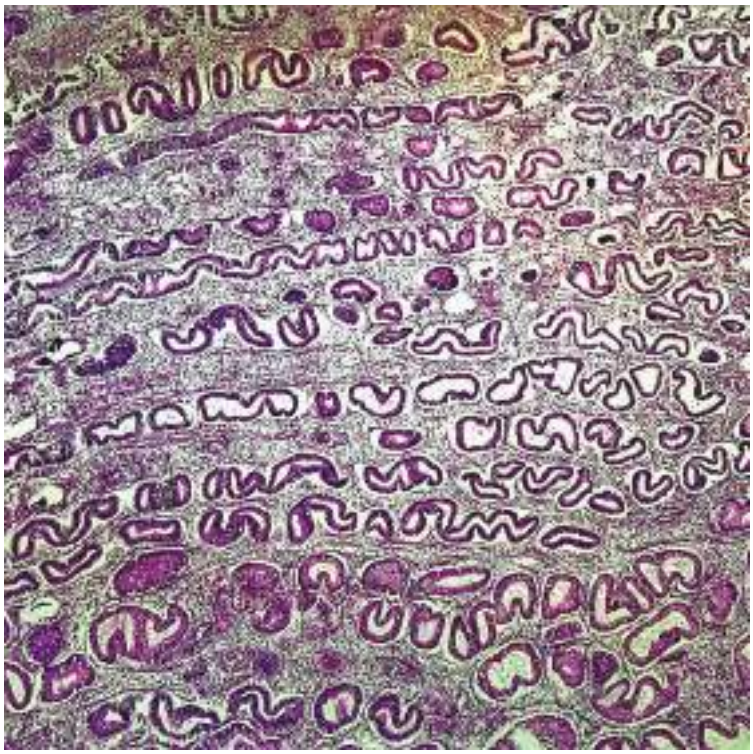
RUBY O. RUSIA-UY
Gram stain of cervicovaginal smear
What am I? It depends...
To a kid, a teddy bear.
To an animal lover, a koala or a tarsier.
To a parasitologist, a scolex.
To a mystery hunter, an ET or an alien.
What do you think am I?
Just a bunch of squamous epithelial cells,
says a pathologist.



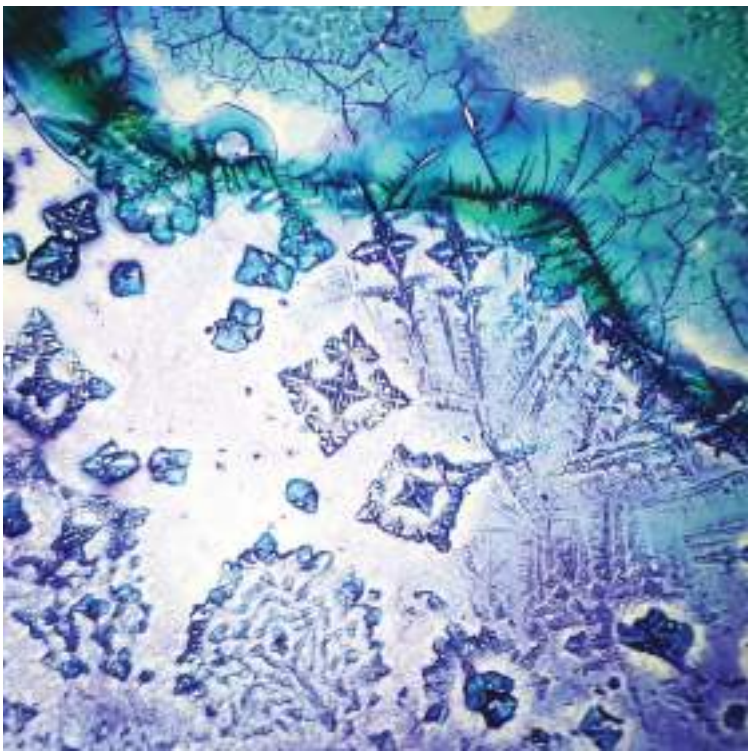
LOUIS ALVIN MARANAN
Incidental finding on a section of lung tissue exhibiting a Coccidioides immitis spherule within a multinucleated giant cell.



RANDELL S. ARIAS
"VAN GOGH"
Bright yellow flecks of hematoidin cystals are strewn across this colonic wall in a patient with aortoenteric fistula redolent of a madman/genius post-impressionist painter's most iconic work 'The Starry Night'.

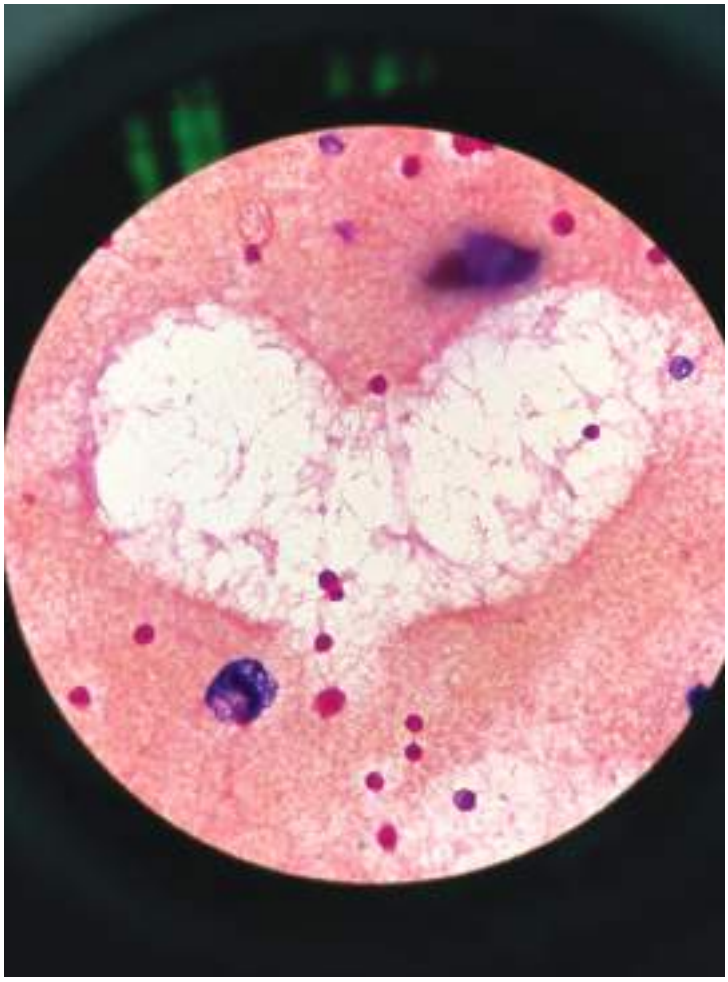


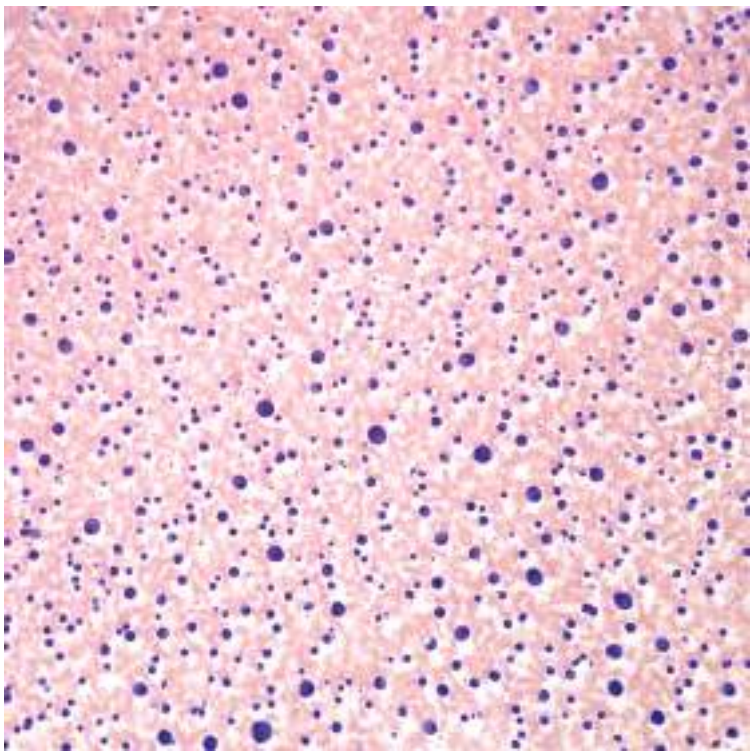
PHILIP TEOMAR A. RADIN II
The picture depicts an endometrial tissue in secretory phase composed of layers of long, tortuous to serrated glands looking like gummy worms, lined by cells with short rounded nuclei with some subnuclear vacuoles and intraluminal secretions. These are supported by a fairly loose stroma.



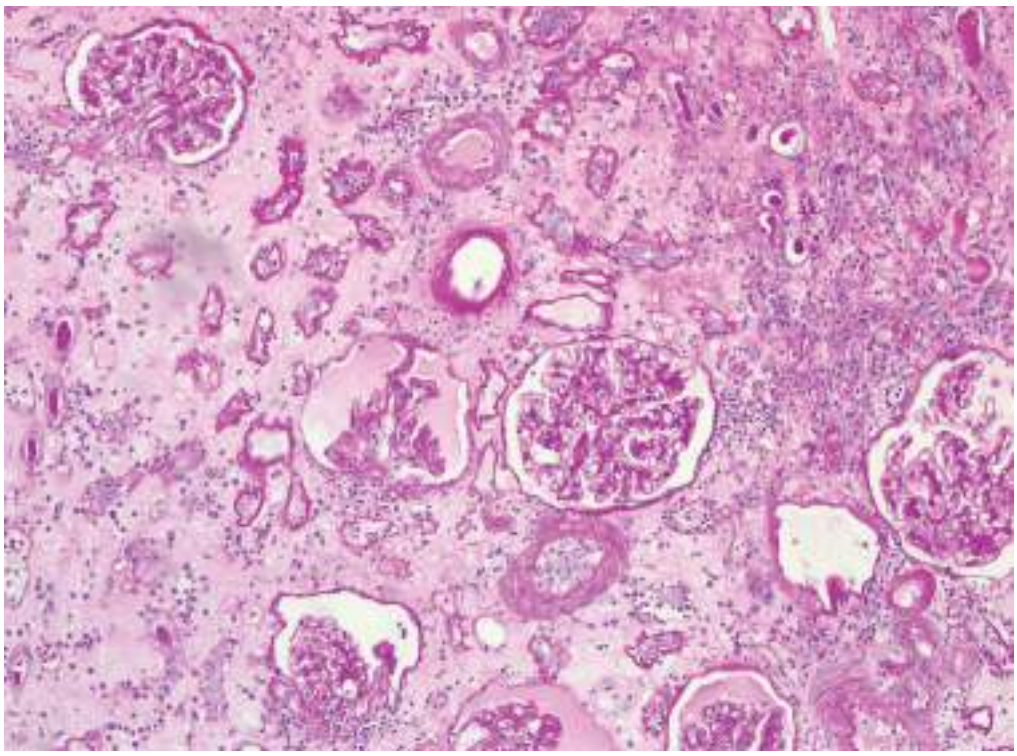
FRANZ JOBERT L. SEBASTIAN
This image depicts crystals from a parotid cyst smear.

EVELINA N. LAGAMAYO
"A HEART DOWN ON ITS KNEES"
What a big surprise when on Valentine's Day! I saw this heart-shaped image from a gram stain of synovial fluid knee aspirate from an arthritic patient. I went home with a happy heart because I see love even at work



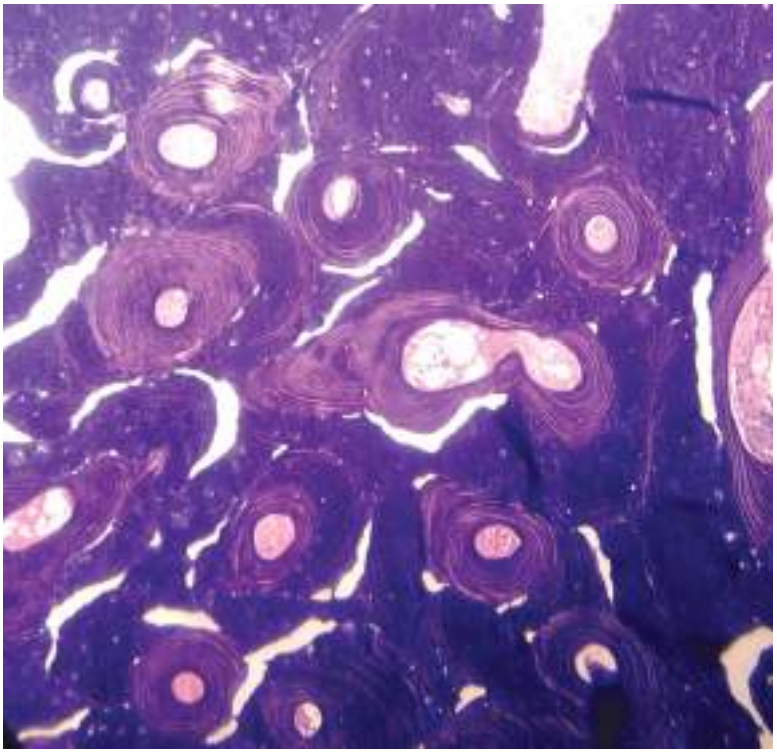


OTHANIEL PHILIP R. BALISAN
"PURPLE RAIN"
These cytological smear shows a flurry of purple 'blobs' or benign mesothelial cells which is a usual diagnostic stumbling block for the uninitiated.

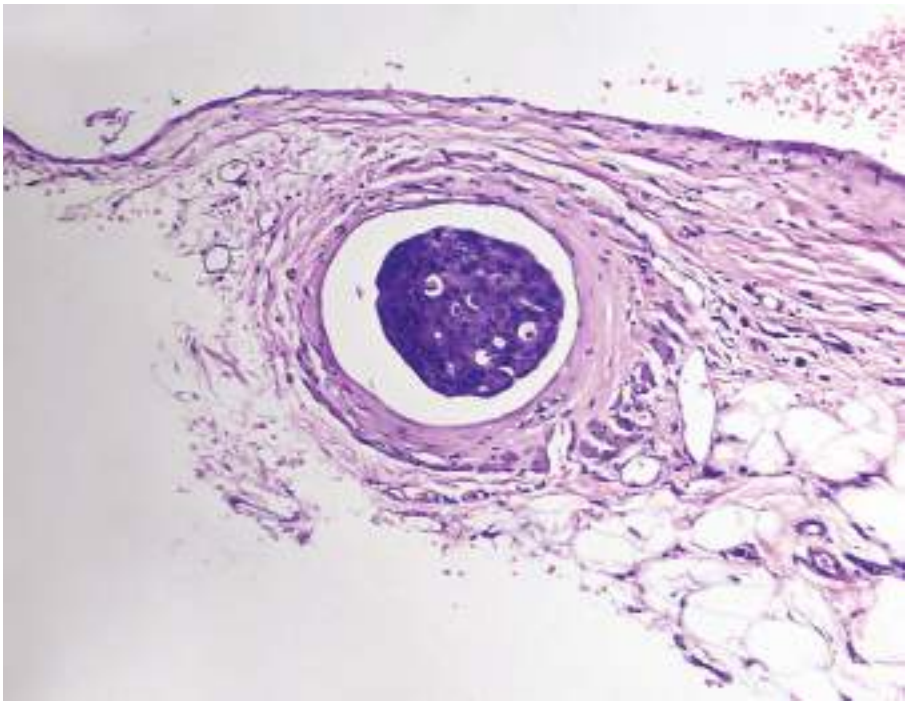


AARON PIERRE P. CALIMAG
"KAPIT LANG"
This photo is from a renal allograft with acute T-cell mediated rejection with a chronic active component. There are areas of inflammation, sclerosis, and hemorrhage. It shows that despite how everything else falls apart around you, you still manage to muster the strength to hold on.

CHRISTOPHER ALEC A. MAQUILING
"BEWARE OF FAKE NEWS"
This is a photomicrograph (40x magnification) of a worm taken from a stool sample from an adult male that was initially suspected as a parasite. On further investigation, it turned out to be a larvae of drain flies (Order: Diptera, Family: Psychodidae) that bred in his toilet bowl. Fake (and very fortunate) news, indeed.



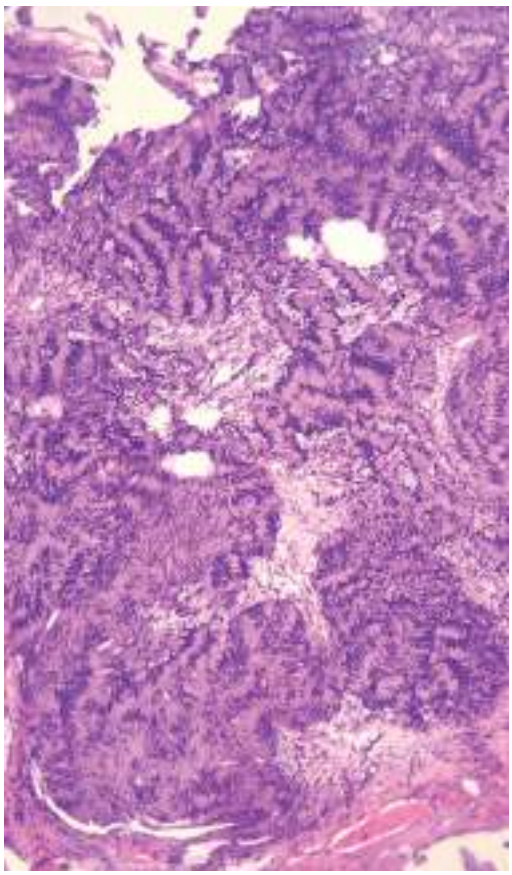
WALDEMAR SIY
A microscopic sneak peak of the universe, of its countless galaxies and stars, hiding within us.

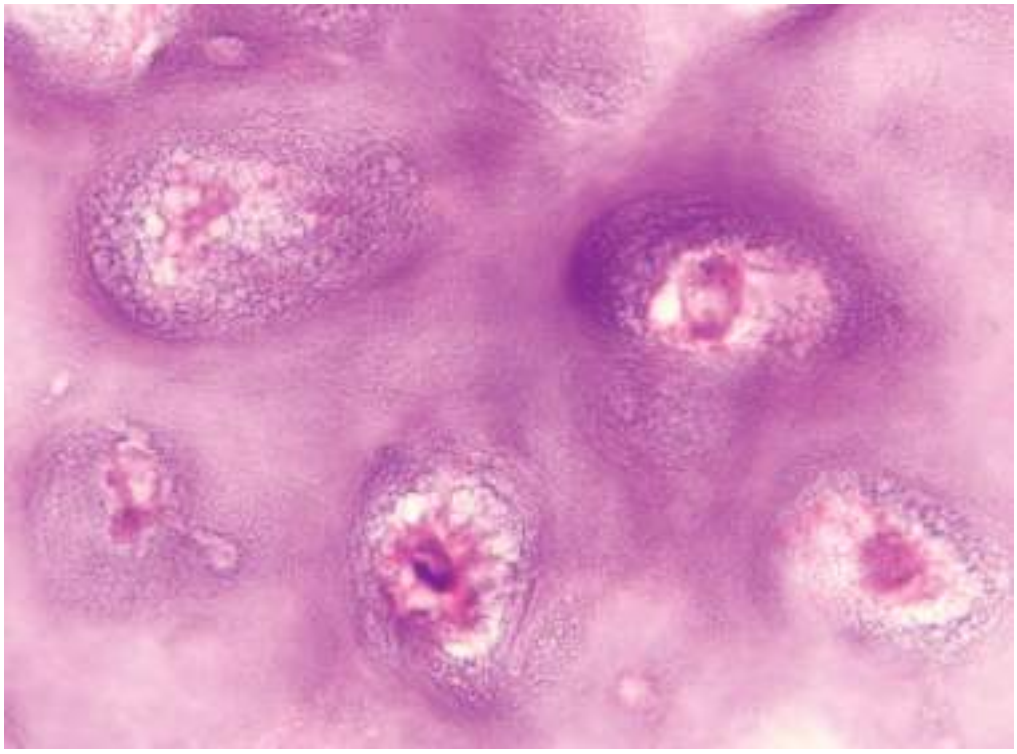


THIRD PLACE

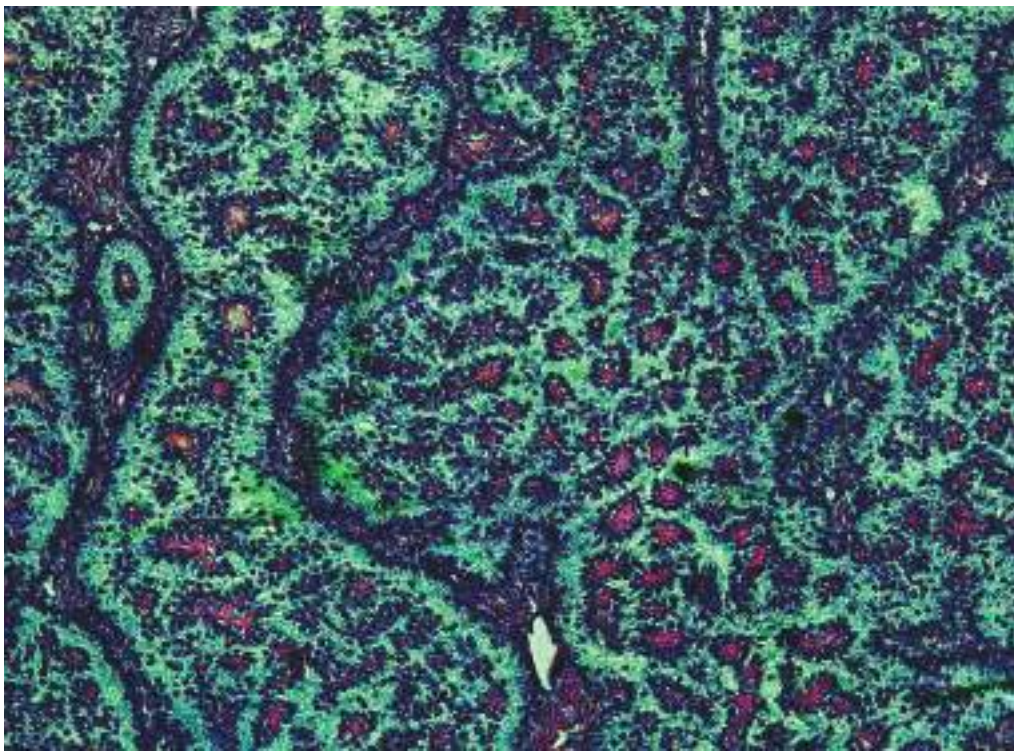
NIKKO PAOLO R. CABLAO
"BON VOYAGE!"
A photomicrograph of lymphovascular space invasion from an invasive mammary carcinoma in a 50-year-old female. A ball of tumor cells is seen inside a blood vessel all set for an adventure to the great unknown. Any guesses where these guys could end up?

ANDREA R. VILLARUEL
"SO CLASSICAL... IT LOOKS UNUSUAL!"
Tumors want to be diagnosed. Look at the wild animal stripes in this cerebellopontine angle schwannoma. Sometimes... the horses are zebras!

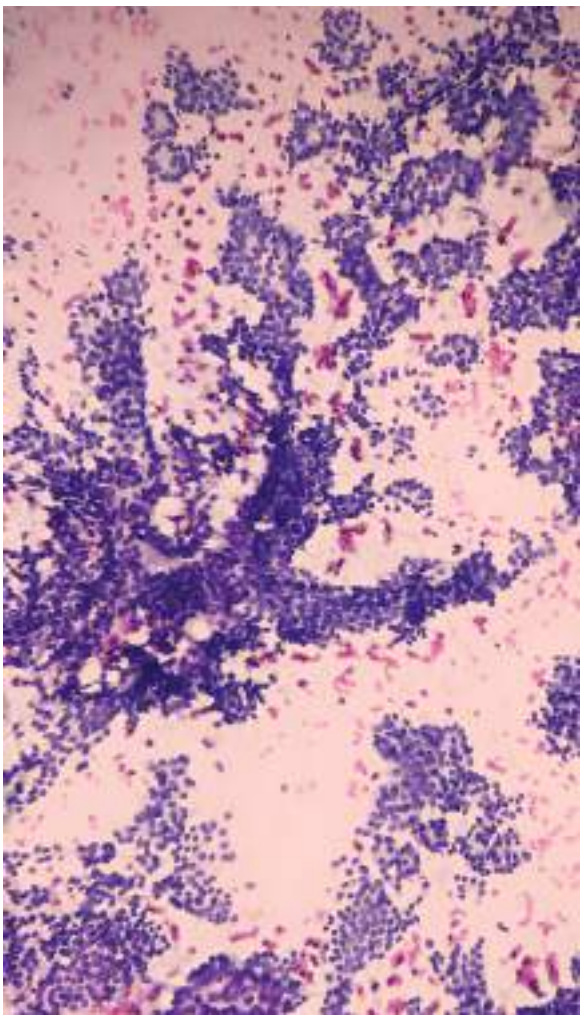




GLENN NATHANIEL SAN DIEGO VALLOSO
Olympus 5-header microscope with camera under oil-immersion objective.Narrative of the image: An excised, solitary, slow-growing, painless, firm single nodular neck mass from an adult male.



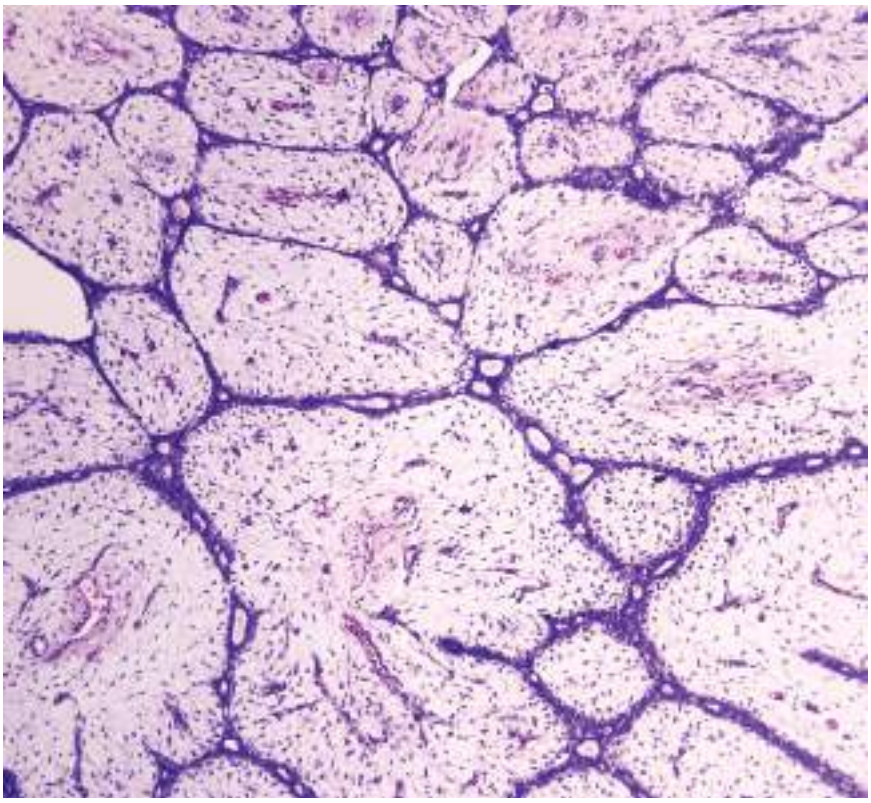
DEMIE DANE C. SANORIA
Granulosa Cell Tumors form characteristic "Cal Exner Bodies", comprised of a single layer of granulosa cells forming "gland-like" structures containing acidophilic material. Green hues and filters were added to contrast with the purple staining nuclei and pinkish material contained within these structures, resembling rose bushes in a luminescent garden.



CRISTON VAN C. MANASAN
"PAP ON PAPS"
Papillary Thyroid Carcinoma
on Papanicolaou Stain

CHRISTINE MAE OLIVAR
"TOGE"
Toge sa kanyang dumi!
Dahan-dahang lumalaki.
Kumekembot unti-unti,
Para maging ispageti.

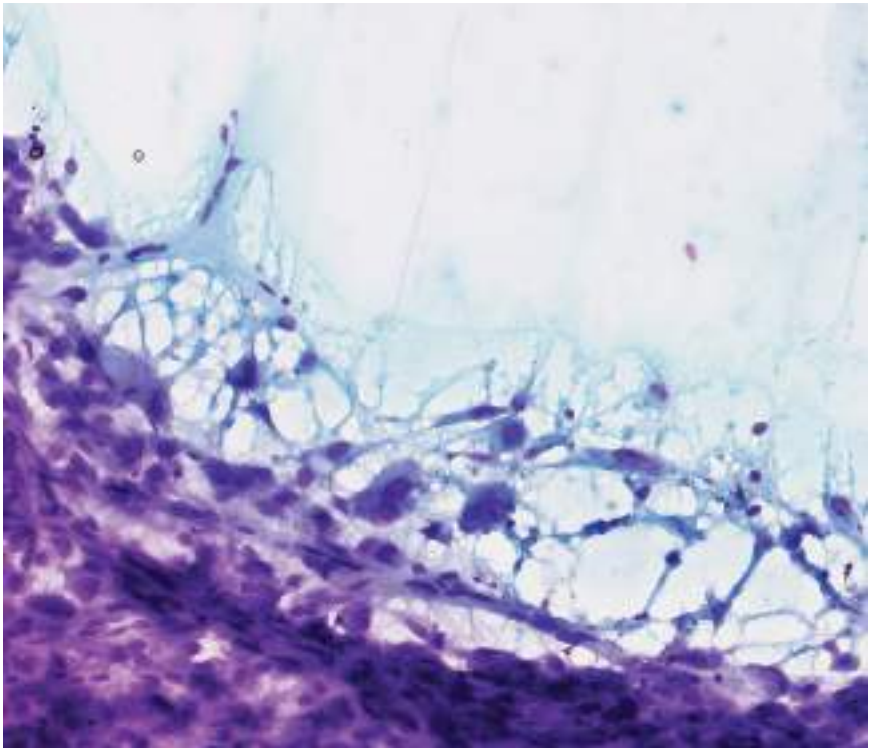
Hatching of Ascaris lumbricoides
Olympus CX23, 100x magnification

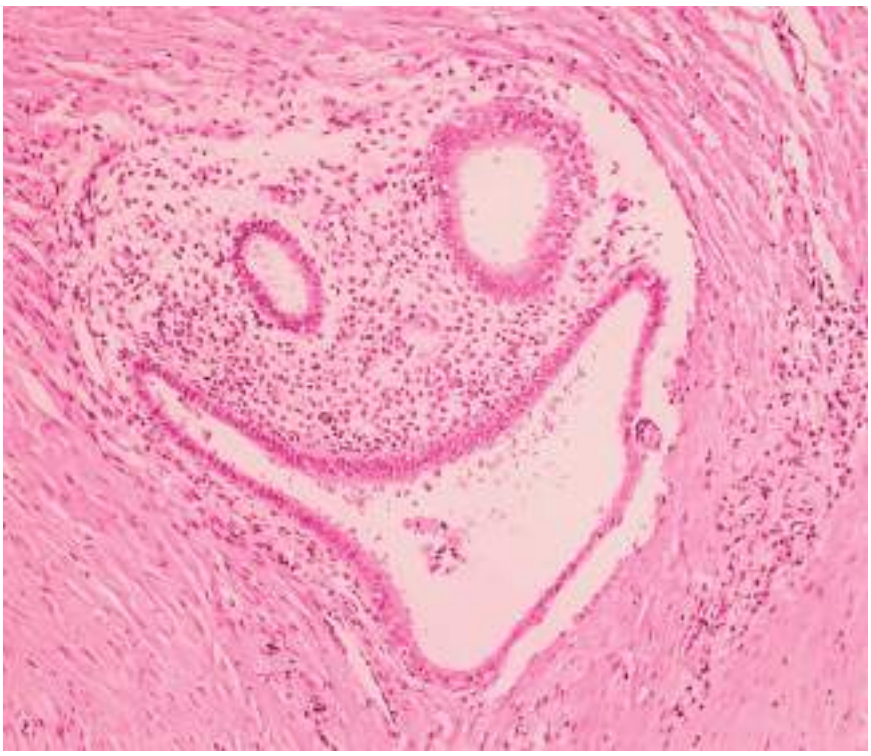


GABRIEL M. OZOA
"COBBLESTONES"
A breast mass from a young adult female.

JOEANNE SALISE
"WAVES"
Angry waves in the ocean.
A stormy daylight.
The predator is not here.
But the creatures are in fear.

(Cytology of subependymal giant cell astrocytoma)

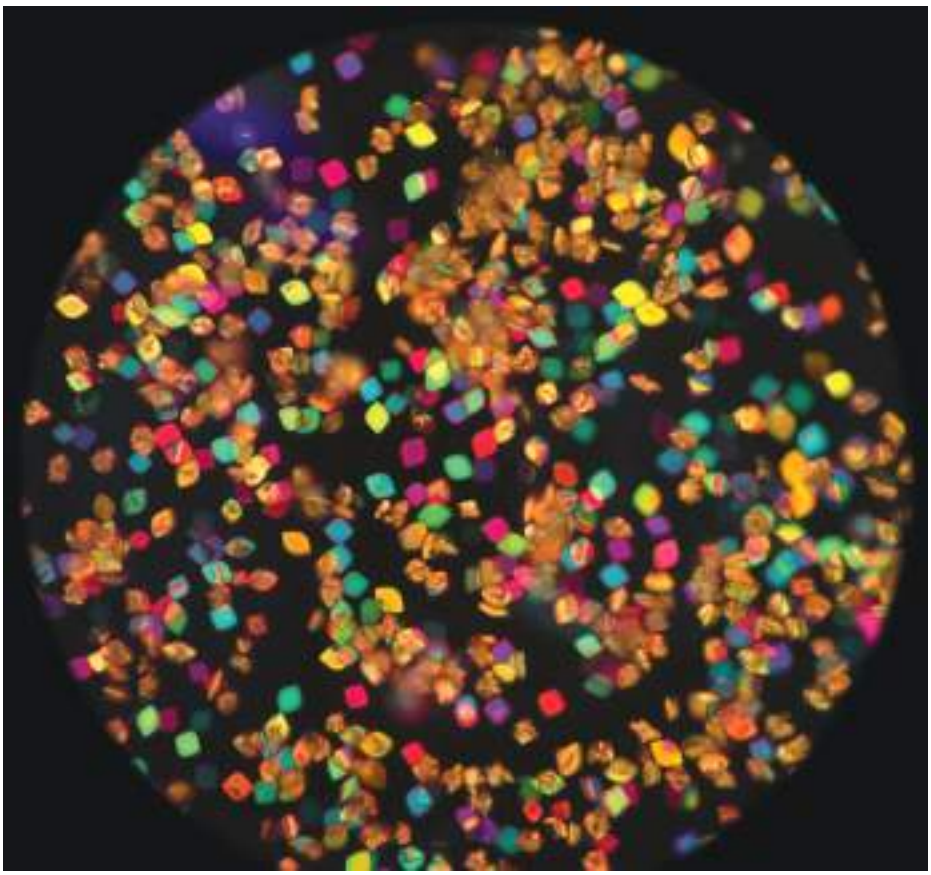


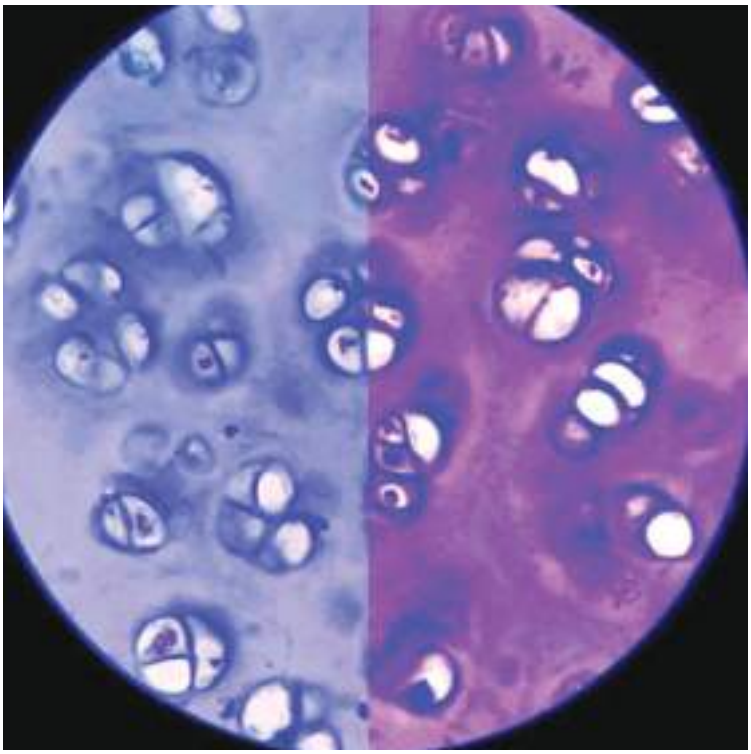


LESTER FLOYD D. ZAMORA
"THE SINISTER SMILE OF PAIN"
The sinister smile that can make even the strongest woman bow down in pain - Oh! how could you endometriosis?

FIRST PLACE

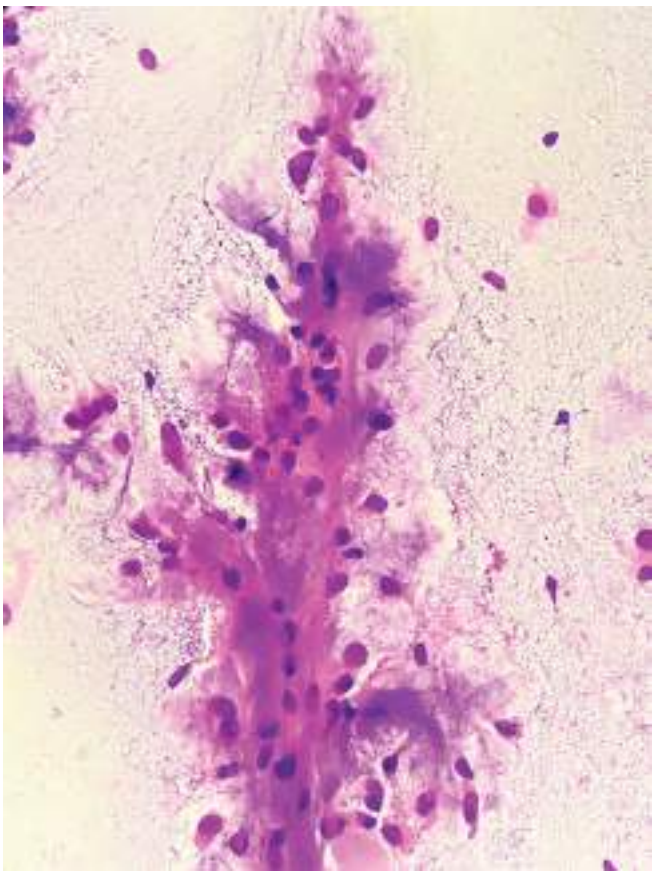
OLIVER D. PINTOR
"PIXIE DUST"
Details of the microscope and technique:
Human urine uric acid crystals under an Olympus CX31-P Polarizing Microscope, 40x magnification.
"The human body is made from a sprinkle of love, a dash of hope, and a little bit of pixie dust...

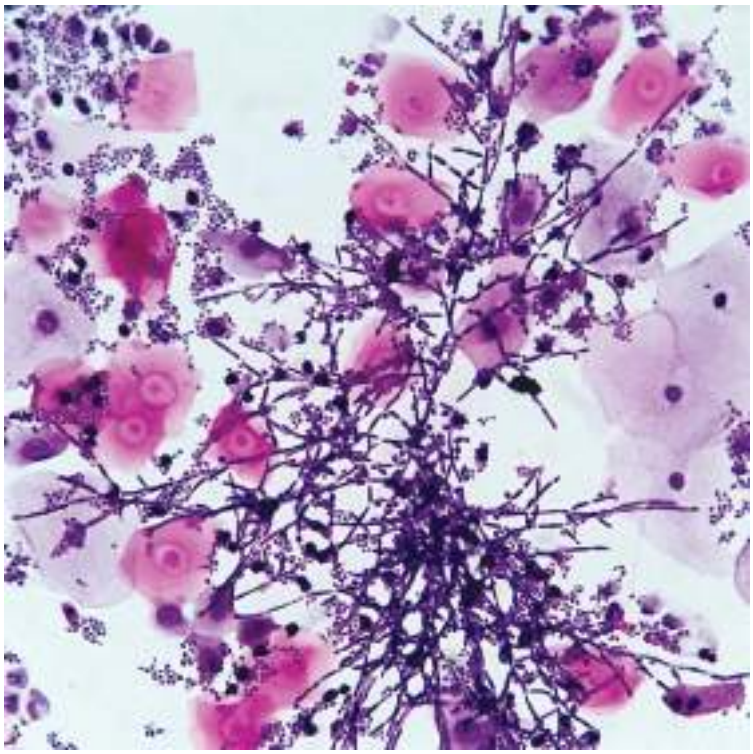




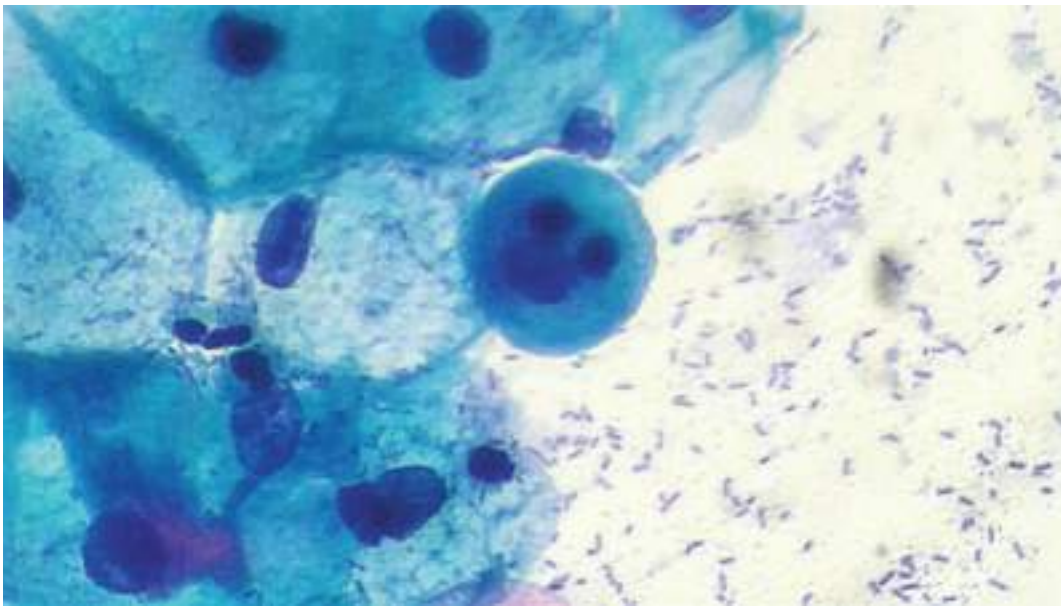
JOSEPH MICHAEL R. ESPIRITU
"VARYING SHADES OF BLUE"
The interplay of different stains: Masson trichrome and H&E with Alcian blue, bequeaths beautiful hues of this simple hyaline cartilage. Notice the beautiful blue hue of the left section elicited by Masson trichrome; while on the right, the Alcian blue outlines the lacunae on an H&E background.

VICTORIA E. CRUZ
This is a smear from a fine needle aspiration biopsy of a pre-auricular mass. The smear consists of bland epithelial cells entangled with a fibrillar matrix. Diagnosis: Pleomorphic Adenoma.





PHILIPPINE HEART CENTER
"GROWING GARDEN"
'Mary, Mary, quite contrary, how does your garden grow?'.
Antibiotic use, uncontrolled diabetes, and
elevated estrogen, among other things.



Arnel Christian K. Dy
UNIVERSITY OF THE EAST RAMON MAGSAYSAY MEDICAL CENTER
"Spot the Hidden Mickey!"

PHILIPPINE JOURNAL OF PATHOLOGY

Instructions to Authors

The **Philippine Journal of Pathology (PJP)** is an open-access, peer-reviewed, English language, medical and health science journal that is published continuously online and semi-annually in print by the Philippine Society of Pathologists, Inc. (PSP, Inc). All manuscripts must be submitted through the PJP Official Website (Open Journal Systems) (http://philippinejournalofpathology.org). All other correspondences and other editorial matters should be sent via electronic mail to philippinepathologyjournal@gmail.com.

Articles and any other material published in the PJP represent the work of the author(s) and do not reflect the opinions of the Editors or the Publisher. **Articles that do not subscribe to the Instructions to Authors shall be promptly returned.**

ARTICLE SECTIONS

The PJP welcomes manuscripts on all aspects of pathology and laboratory medicine, to include cytology, histopathology, autopsy, forensic pathology, clinical chemistry, clinical microscopy, medical microbiology, parasitology, immunology, hematology, blood banking, medical technology, laboratory diagnostics, laboratory biosafety and biosecurity, laboratory management, and quality assurance.

The PJP accepts original articles, review articles, case reports, feature articles, brief communications, autopsy cases, editorials, or letters to the Editor.

Original articles

The research must have received institutional review board approval that is explicitly stated in the methodology. The abstract should contain no more than 200 words with a structured format consisting of the objective/s, methodology, results and conclusion. A manuscript for original articles should not exceed 25 typewritten pages (including tables, figures, illustrations and maximum of 30 references) or 6000 words.

Reviews

Review articles, both solicited and unsolicited, provide information on the "state of the art." PJP reviews not only summarize current understanding of a particular topic but also critically appraise relevant literature and data sources, describe significant gaps in the research, and future directions. The abstract should be from 50 to 75 words and should not be structured. A manuscript for reviews should not exceed 15 typewritten pages (including tables, figures, illustrations and maximum of 50 references) or 4000 words.

Case Reports

This type of article pertains to single or multiple reports of well-characterized cases that are highly unusual, novel, or rare; or with a unique or variant presentation, evolution or course; or that represent an unexpected or uncommon association of two or more diseases or disorders that may represent a previously unsuspected causal relationship; or that are underreported in the literature. The abstract should be from 50 to 75 words and should not be structured. A manuscript for case reports should not exceed 10 typewritten pages (including tables, figures, illustrations and maximum of 15 references) or 3000 words.

Feature articles

The PJP may feature articles, either as part of an issue theme or a special topic on pathology by a local or international expert or authority. The abstract should be from 50 to 75 words and should not be structured. A manuscript for feature articles should not exceed 25 typewritten pages (including tables, figures, illustrations and maximum of 30 references) or 6000 words.

Autopsy Vault

The PJP highly welcomes articles on autopsy protocols of cases. The article must include a summary presentation of the history, evaluation and work-up, clinical course of a case, followed by the autopsy procedure performed, gross and microscopic findings, discussion, learning points and conclusion. The PJP recognizes the instructional and educational value of articles under this section. The abstract should be from 50 to 75 words and should not be structured. A manuscript for the Autopsy Vault should not exceed 25 typewritten pages (including tables, figures, illustrations and maximum of 30 references) or 6000 words.

Images in Pathology

Images of unique, interesting, or highly educational cases encountered in hematology, cytology, histopathology, or medical microbiology, may be submitted under this section, and may include photomicrographs, gross pictures, machine read-outs, among others. A brief history, the photograph(s) and short discussion of the case. No abstract is required. A manuscript for Images in Pathology should not exceed 500 words, with maximum of 10 references. This is distinct from the Case Report which is a full write up.

Brief Communications

Brief Communications are short reports intended to either extend or expound on previously published research or present new and significant findings which may have a major impact in current practice. If the former, authors must acknowledge and cite the research which they are building upon. The abstract should be from 50 to 75 words and should not be structured. A manuscript for brief communications should not exceed 5 typewritten pages (including tables, figures, illustrations and maximum of 10 references) or 1500 words.

Editorials

Recognized leaders in the field of pathology and laboratory medicine may be invited by the Editor-in-Chief/Editorial Board to present their scientific opinion and views of a particular topic within the context of an issue theme or issues on scholarly publication. No abstract or keywords necessary.

Letters to the Editor

PJP welcomes feedback and comments on previously published articles in the form of Letters to the Editor.
No abstract or keywords are necessary. A Letter to the Editor must not exceed 2 typewritten pages or 500 words.

Special Announcements

Special announcements may include upcoming conventions, seminars or conferences relevant to pathology. The Editors shall deliberate and decide on acceptance and publication of special announcements. Please coordinate with the Editorial Coordinator for any request for special announcements.

COVER LETTER

A cover letter must accompany each manuscript citing the complete title of the manuscript, the list of authors (complete names, position/designation and institutional affiliations), with one (1) author clearly designated as corresponding author, providing his/her complete institutional mailing address, institutional telephone/fax number, and work e-mail address. The **PJP Cover Letter Template** must be used.

PJP AUTHOR FORM

For submissions to the PJP to be accepted, all authors must read and sign the **PJP Author Form** consisting of: (1) the Authorship Certification, (2) the Author Declaration, (3) the Statement of Copyright Transfer, and (4) the Statement of Disclosure of Conflicts of Interest. The completely accomplished PJP Author Form shall be scanned and submitted along with the manuscript. No manuscript shall be received without the PJP Author Form.

GENERAL FORMATTING GUIDELINES

- Authors must use the standard PJP templates for each type of manuscript. These templates are aligned with the most current versions of the EQuaToR Network guidelines and checklists (http://equatornetwork.org).
- The manuscript should be encoded on the template using Microsoft Word (2007 version or later version), single-spaced, 2.54 cm margins throughout, on A4 size paper. Preferred fonts may include Century Gothic (template default), Times New Roman, or Arial.
- The manuscript should be arranged in sequence as follows: (1) Title Page, (2) Abstract, (3) Text, (4) References, (5) Tables, and (6) Figures & Illustrations.
- All the sheets of the manuscript should be labelled with the page number (in Hindu-Arabic Numerals) printed on the upper right corner.
- References should pertain directly to the work being reported. Within the text, references should be indicated using Hindu-Arabic numerals in superscripts.

SPECIFIC FORMATTING GUIDELINES

Title and Authors

- The title should be as concise as possible.
- A running title (less than 50 characters) shall also be required. The running title is the abbreviated version of the title that will be placed in the header. The running title should capture the essence of the manuscript title.
- The full name of the author(s) directly affiliated with the work should be included (First name, Middle initial and Last name). The order of authorship shall be the prerogative of the author(s).
- There are 4 criteria for authorship (ICMJE recommendations). These are captured in the **PJP Author Form**.
  - **Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND**
  - **Drafting the work or revising it critically for important intellectual content; AND**
  - **Final approval of the version to be published; AND**
  - **Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.**
- The highest educational attainment or title of the authors should be included as an attachment whenever appropriate (MD, PhD, et cetera).
- Name and location of no more than one (1) institutional affiliation per author may be included.
- If the paper has been presented in a scientific forum or convention, a note should be provided indicating the name of the forum or convention, location (country), and date of its presentation.

Abstract

- **For manuscripts under the "Original Article" section:** the abstract should contain no more than 300 words with a structured format consisting of the following standard headings: objective/s, methodology, results and conclusion.
- **For manuscripts under the "Feature Article," "Review Article," "Case Report," "Brief Communications," and "Autopsy Vault" sections:** the abstract should be no more than 200 words and need not be structured.
- Letters to the Editor and editorials do not require an abstract.

Keywords

At least three (3) keywords but no more than six (6), preferably using terms from the **Medical Subject Headings (MeSH) list of Index Medicus,** should be listed horizontally under the abstract for cross-indexing of the article.

Text

- The text should be organized consecutively as follows: **Introduction, Methodology, Results and Discussion, Conclusion** (IMRaD format), followed by **Disclosures, Acknowledgments** and **References.**
- All references, tables, figures and illustrations should be cited in the text, in numerical order.
- All abbreviations should be spelled out once (the first time they are mentioned in the text) followed by the abbreviation enclosed in parentheses. The same abbreviation may then be used subsequently instead of the full names.
- All measurements and weights should be in System International (SI) units.
- Under **Methodology**, information should be provided on institutional review board/ethics committee approval or informed consent taking (if appropriate).
- **Acknowledgements** to individuals/groups of persons, or institution/s who have contributed to the manuscript but *did not qualify as authors* based on the ICMJE criteria, should be included at the end of the text just before the references. Grants and subsidies from government or private institutions should also be acknowledged.

References

- References in the text should be identified by Hindu-Arabic Numerals in superscript on the same line as the preceding sentence.
- References should be numbered consecutively in the order by which they are mentioned in the text. They should not be alphabetized.
- All references should provide inclusive page numbers.
- Journal abbreviations should conform to those used in PubMed.
- A maximum of six authors per article can be cited; beyond that, name the first three and add "et al."
- The style/punctuation approved by PJP conforms to that recommended by the International Committee of Medical Journal Editors (ICMJE) available at http://www.icmje.org. Examples are shown below:

One to Six Authors

Krause RM. The origin of plagues: old and new. *Science*. 1992;257:1073-1078.

Mokdad AH, Bowman BA, Ford ES, Vinicor F, Marks JS, Koplan JP. The continuing epidemics of obesity and diabetes in the US. JAMA. 2001;286(10):1195-1200.

More than Six Authors

Rhynes VK, McDonald JC, Gelder FB, et al. Soluble HLA class I in the serum of transplant recipients. Ann Surg. 1993; 217 (5): 485–9.

Authors Representing a Group

Moher D, Schulz KF, Altman D; for the CONSORT Group. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. JAMA. 2001;285(15):1987-1991.

Book

Byrne, DW. Publishing your medical research paper: What they don't teach in medical school. Baltimore: Williams & Wilkins, 1998.

World Wide Web

Barry JM. The site of origin of the 1918 influenza pandemic and its public health implications. [Commentary]. JTranslational Med. January 20, 2004;2(3):1-4. http://www.translational-medicine.com/content/2/1/3. Accessed November 18, 2005.

Tables

- Cite all tables consecutively in the text and number them accordingly.
- Create tables preferably using Microsoft Excel with one table per worksheet.
- Tables should not be saved as image files.
- The content of tables should include a table number (Hindu-Arabic) and title in capital letters above the table.
- Place explanatory notes and legends, as well as definitions of abbreviations used below the table. For legends, use small letters (i.e., a, b, c, d).
- Each table must be self-explanatory, being a supplement rather than a duplicate of information in the text.
- Up to a maximum of five (5) tables are allowed.

Figures and Graphs

- Figures or graphs should be identified by Hindu-Arabic Numeral/s with titles and explanations underneath.
- The numbers should correspond to the order in which the figures/graphs occur in the text.
- Figures & graphs should not be saved as image files. For illustrations and photographs, see next section.
- Provide a title and brief caption for each figure or graph. Caption should not be longer than 15-20 words.
- All identifying data of the subject/s or patient/s under study such as name or case numbers, should be removed.
- Up to a maximum of five (5) figures and graphs are allowed.

Illustrations and Photographs

- Where appropriate, all illustrations/photographic images should be at least 800 x 600 dpi and submitted as image files (preferably as .png, .jpeg or .gif files).
- For photomicrographs, the stain used (e.g. H & E) and magnification (e.g. X400) should be included in the description.
- Computer-generated illustrations which are not suited for reproduction should be professionally redrawn or printed on good quality laser printers. Photocopies are not acceptable.
- All letterings for illustration should be of adequate size to be readable even after size reduction.
- Place explanatory notes and legends, as well as definitions of abbreviations used below the illustration/photograph.
- Up to a maximum of five (5) illustrations/ photographs are allowed.

N.B.: For tables, figures, graphs, illustrations and photographs that have been previously published in another journal or book, a note must be placed under the specific item stating that such has been adapted or lifted from the original publication. This should also be referenced in the **References** portion.

EDITORIAL PROCESS (Figure 1)

- The Editorial Coordinator shall review each submission to check if it has met aforementioned criteria and provide feedback to the author within 24 hours.
- Once complete submission is acknowledged, the manuscript undergoes Editorial Board Deliberation to decide whether it shall be considered or not for publication in the journal. Within five (5) working days, authors shall be notified through e-mail that their manuscript either (a) has been sent to referees for peer-review or (b) has been declined without review.
- The PJP implements a strict double blind peer review policy. For manuscripts that are reviewed, authors can expect a decision within ten (10) working days from editorial deliberation. There may be instances when decisions can take longer: in such cases, the Editorial Coordinator shall inform the authors.
- The editorial decision for manuscripts shall be one of the following: (a) acceptance without further revision, (b) acceptance with minor revisions, (c) major manuscript revision and resubmission, or (d) non-acceptance.
- Accepted manuscripts are subject to editorial modifications to bring them in conformity with the style of the journal. Copyediting and layout shall take five (5) working days, after which the manuscript is published online.
- All online articles from the last six (6) months shall be collated and published in print as a full issue.

EDITORIAL OFFICE CONTACT INFORMATION:

The Philippine Journal of Pathology
2nd Floor, Laboratory Research Division
Research Institute for Tropical Medicine
Filinvest Corporate City
Alabang, Muntinlupa City 1781
Editor-in-Chief: **Amado O. Tandoc III, MD, FPSP**
Telefax number: (+632)8097120
E-mail: philippinepathologyjournal@gmail.com
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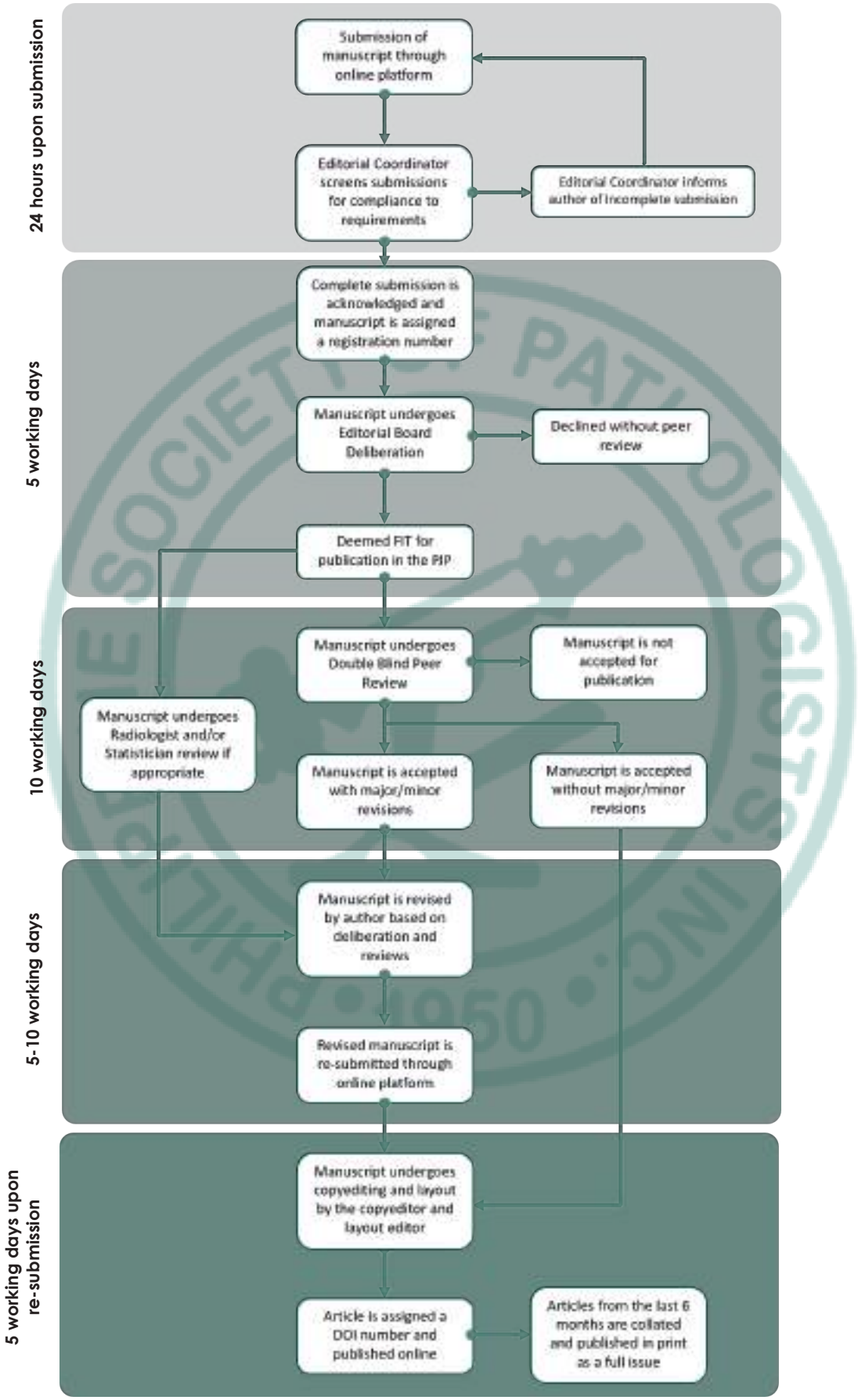

Figure 1. Editorial Process Flow.

PHILIPPINE JOURNAL OF PATHOLOGY
PJP

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COMPLETE TITLE OF MANUSCRIPT

_____

_____

_____

AUTHORSHIP CERTIFICATION

☐ In consideration of our submission to the Philippine Journal of Pathology (PJP), the undersigned author(s) of the manuscript hereby certify, that all of us have actively and sufficiently participated in (1) the conception or design of the work, the acquisition, analysis and interpretation of data for the work; AND (2)drafting the work, revising it critically for important intellectual content; AND (3) that we are all responsible for the final approval of the version to be published; AND (4) we all agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

AUTHOR DECLARATIONS

☐ The undersigned author(s) of the manuscript hereby certify, that the submitted manuscript represents original, exclusive and unpublished material. It is not under simultaneous consideration for publication elsewhere. Furthermore, it will not be submitted for publication in another journal, until a decision is conveyed regarding its acceptability for publication in the PJP.

☐ The undersigned hereby certify, that the study on which the manuscript is based had conformed to ethical standards and/or had been reviewed by the appropriate ethics committee.

☐ The undersigned likewise hereby certify that the article had written/informed consent for publication from involved subjects (for case report/series only) and that in case the involved subject/s can no longer be contacted (i.e., retrospective studies, no contact information, et cetera), all means have been undertaken by the author(s) to obtain the consent.

AUTHOR STATEMENT OF COPYRIGHT TRANSFER

☐ Furthermore, the undersigned author(s) recognize that the PJP is an OPEN-ACCESS publication which licenses all published manuscripts to be used for building on and expanding knowledge, for non-commercial purposes, so long as the manuscripts are properly cited and recognized (Attribution-NonCommercial-ShareAlike 4.0 International Creative Commons License [CC BY-NC-SA 4.0]. The undersigned author(s) hereby, transfer/assign or otherwise convey all copyright ownership of the manuscript to the PJP.

AUTHOR DISCLOSURE OF CONFLICTS OF INTEREST

In order to ensure scientific objectivity and independence, the PJP requires all authors to make a full disclosure of areas of potential conflict of interest. Such disclosure will indicate whether the person and/or his/her immediate family has any financial relationship with pharmaceutical companies, medical equipment manufacturers, biomedical device manufacturers, or any companies with significant involvement in the field of health care. Place all disclosures in the table below. An extra form may be used if needed.

Examples of disclosures include but not limited to: ownership, employment, research support (including provision of equipment or materials), involvement as speaker, consultant, or any other financial relationship or arrangement with manufacturers, companies or suppliers. With respect to any relationships identified, author(s) must provide sufficiently detailed information to permit assessment of the significance of the potential conflict of interest (for example, the amount of money involved and/or the identification of any value of goods and services).

AUTHOR NAME	RELATIONSHIP	MANUFACTURER/ SUPPLIER/ COMPANY

All disclosures shall remain confidential during the review process and the nature of any final printed disclosure will be determined by the PJP. If there are no conflicts of interest to disclose, the author(s) should check the box below.

☐ I/We do not have any conflicts of interest to disclose.

Author Name	Signature	Date (MM/DD/YYYY)
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

ICMJE Form for Disclosure of Potential Conflicts of Interest

Instructions

The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. The form is designed to be completed electronically and stored electronically. It contains programming that allows appropriate data display. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in six parts.

1. Identifying information.

2. The work under consideration for publication.

This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking "No" means that you did the work without receiving any financial support from any third party -- that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check "Yes".

3. Relevant financial activities outside the submitted work.

This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. You should disclose interactions with ANY entity that could be considered broadly relevant to the work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

4. Intellectual Property.

This section asks about patents and copyrights, whether pending, issued, licensed and/or receiving royalties.

5. Relationships not covered above.

Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.

Definitions.

Entity: government agency, foundation, commercial sponsor, academic institution, etc.
Grant: A grant from an entity, generally [but not always] paid to your organization
Personal Fees: Monies paid to you for services rendered, generally honoraria, royalties, or fees for consulting , lectures, speakers bureaus, expert testimony, employment, or other affiliations
Non-Financial Support: Examples include drugs/equipment supplied by the entity, travel paid by the entity, writing assistance, administrative support, etc.
Other: Anything not covered under the previous three boxes
Pending: The patent has been filed but not issued
Issued: The patent has been issued by the agency
Licensed: The patent has been licensed to an entity, whether earning royalties or not
Royalties: Funds are coming in to you or your institution due to your patent

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name) _____
2. Surname (Last Name) _____
3. Date _____

4. Are you the corresponding author? ☐ Yes ☐ No

5. Manuscript Title _____

6. Manuscript Identifying Number (if you know it) _____

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☐ No

ADD

Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were **present during the 36 months prior to publication**.

Are there any relevant conflicts of interest? ☐ Yes ☐ No

ADD

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☐ No

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 5. Relationships not covered above

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

☐ Yes, the following relationships/conditions/circumstances are present (explain below):

☐ No other relationships/conditions/circumstances that present a potential conflict of interest

At the time of manuscript acceptance, journals will ask authors to confirm and, if necessary, update their disclosure statements. On occasion, journals may ask authors to disclose further information about reported relationships.

Section 6. Disclosure Statement

Based on the above disclosures, this form will automatically generate a disclosure statement, which will appear in the box below.

Generate Disclosure Statement

Evaluation and Feedback

Please visit http://www.icmje.org/cgi-bin/feedback to provide feedback on your experience with completing this form.

PHILIPPINE JOURNAL OF PATHOLOGY
PJP

PATIENT CONSENT FORM

For case report and image submissions to the PJP to be accepted, the author/s must ensure that patients or patients' legal guardian/relative have provided informed consent to publish information about them in the journal. The completely accomplished PJP Patient Consent Form shall be scanned and submitted along with the manuscript. No case report and image shall be received without the PJP Consent Form.

Name of person described in article or shown in photograph:_____

_____

Subject matter of photograph or article (brief description):

_____

_____

_____

(The Subject matter of the photograph or article is hereafter termed as the "INFORMATION.")

Title of article:

_____

_____

I, _____ , give my consent for this information
[please insert your full name]

about MYSELF/MY CHILD OR WARD/MY RELATIVE relating to the subject matter
[please underline correct description]

above to appear in the Philippine Journal of Pathology (PJP) subject to its publication policies and ethical standards.

I have seen and read the material to be submitted to the PJP and thoroughly understand the following:

- The Information will be published in the PJP without my name. It is the obligation of the PJP to make all attempts, within its reasonable jurisdiction and authority, to ensure my anonymity.
- The Information may also be placed on the PJP website.
- The PJP shall not allow the Information to be used for advertising or packaging or to be used out of context (i.e., used to accompany an entirely different article or topic).
- I can withdraw my consent at any time before publication, but once the Information has already been sent to press, it is my understanding that it will not be possible to revoke the consent.

Signed:_____ Date:_____
[signature over complete name]

Witness:

Signed:_____ Date:_____
[signature over complete name]

Consolidated criteria for reporting qualitative research (COREQ): A 32-item checklist for interviews and focus groups

No	Item	Guide questions / description
DOMAIN 1: RESEARCH TEAM AND REFLEXIVITY		
Personal Characteristics		
1	Interviewer/facilitator	Which author/s conducted the interview or focus group?
2	Credentials	What were the researcher's credentials? E.g. PhD, MD
3	Occupation	What was their occupation at the time of the study?
4	Gender	Was the researcher male or female?
5	Experience and training	What experience or training did the researcher have?
Relationship with participants		
6	Relationship	Was a relationship established prior to study commencement?
7	Participant knowledge of the interviewer	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research
8	Interviewer characteristics	What characteristics were reported about the interviewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic
DOMAIN 2: STUDY DESIGN		
Theoretical framework		
9	Methodological orientation and Theory	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis
Participant selection		
10	Sampling	How were participants selected? e.g. purposive, convenience, consecutive, snowball
11	Method of approach	How were participants approached? e.g. face-to-face, telephone, mail, email
12	Sample size	How many participants were in the study?
13	Non-participation	How many people refused to participate or dropped out? Reasons?
Setting		
14	Setting of data collection	Where was the data collected? e.g. home, clinic, workplace
15	Presence of non-participants	Was anyone else present besides the participants and researchers?
16	Description of sample	What are the important characteristics of the sample? e.g. demographic data, date
Data Collection		
17	Interview guide	Were questions, prompts, guides provided by the authors? Was it pilot tested?
18	Repeat interview	Were repeat interviews carried out? If yes, how many?
19	Audio/visual recording	Did the research use audio or visual recording to collect the data?
20	Field notes	Were field notes made during and/or after the interview or focus group?
21	Duration	What was the duration of the interviews or focus group?
22	Data saturation	Was data saturation discussed?
23	Transcripts returned	Were transcripts returned to participants for comment and/or correction?
DOMAIN 3: ANALYSIS AND FINDINGS		
Data analysis		
24	Number of data coders	How many data coders coded the data?
25	Description of the coding tree	Did authors provide a description of the coding tree?
26	Derivation of themes	Were themes identified in advance or derived from the data?
27	Software	What software, if applicable, was used to manage the data?
28	Participant checking	Did participants provide feedback on the findings?
Reporting		
29	Quotations presented	Were participant quotations presented to illustrate the themes / findings? Was each quotation identified? e.g. participant number
30	Data and findings consistent	Was there consistency between the data presented and the findings?
31	Clarity of major themes	Were major themes clearly presented in the findings?
32	Clarity of minor themes	Is there a description of diverse cases or discussion of minor themes?

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CARE Checklist (2013) of Information to include when Writing a Case Report

Topic	Item no.	Checklist item description	Reported on page no.
Title	1	The words "case report" should be in the title along with the area of focus	_____
Key Words	2	2 to 5 key words that identify areas covered in this case report	_____
Abstract	3a	Introduction—What is unique about this case? What does it add to the medical literature?	_____
	3b	The main symptoms of the patient and the important clinical findings	_____
	3c	The main diagnoses, therapeutics interventions, and outcomes	_____
	3d	Conclusion—What are the main "take-away" lessons from this case?	_____
Introduction	4	One or two paragraphs summarizing why this case is unique with references	_____
Patient Information	5a	De-identified demographic information and other patient specific information	_____
	5b	Main concerns and symptoms of the patient	_____
	5c	Medical, family, and psychosocial history including relevant genetic information	_____
		(also see timeline)	
	5d	Relevant past interventions and their outcomes	_____
Clinical Findings	6	Describe the relevant physical examination (PE) and other significant clinical findings	_____
Timeline	7	Important information from the patient's history organized as a timeline	_____
Diagnostic Assessment	8a	Diagnostic methods (such as PE, laboratory testing, imaging, surveys)	_____
	8b	Diagnostic challenges (such as access, financial, or cultural)	_____
	8c	Diagnostic reasoning including other diagnoses considered	_____
	8d	Prognostic characteristics (such as staging in oncology) where applicable	_____
Therapeutic Intervention	9a	Types of intervention (such as pharmacologic, surgical, preventive, self-care)	_____
	9b	Administration of intervention (such as dosage, strength, duration)	_____
	9c	Changes in intervention (with rationale)	_____
Follow-up and Outcomes	10a	Clinician and patient-assessed outcomes (when appropriate)	_____
	10b	Important follow-up diagnostic and other test results	_____
	10c	Intervention adherence and tolerability (How was this assessed?)	_____
	10d	Adverse and unanticipated events .	_____
Discussion	11a	Discussion of the strengths and limitations in your approach to this case	_____
	11b	Discussion of the relevant medical literature	_____
	11c	The rationale for conclusions (including assessment of possible causes)	_____
	11d	The primary "take-away" lessons of this case report	_____
Patient Perspective	12	When appropriate the patient should share their perspective on the treatments they received	_____
Informed Consent	13	Did the patient give informed consent? Please provide if requested	☐ Yes ☐ No

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PRISMA 2009 Checklist of Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Section / Topic	Item no.	Checklist item	Reported on page no.
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	_____
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	_____
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	_____
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	_____
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	_____
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	_____
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	_____
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	_____
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	_____
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	_____
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	_____
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	_____
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	_____
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	_____
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	_____
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	_____
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	_____
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	_____
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	_____
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	_____
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	_____
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	_____
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	_____
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	_____
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	_____
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	_____
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	_____

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097. For more information, visit: www.prisma-statement.org.

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STROBE Statement - Checklist of Items that should be included in Reports of Observational Studies

Section / Topic	Item no.	Recommendation
TITLE		
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found
INTRODUCTION		
Background / rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
METHODS		
Study Design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(a) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants (b) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data Sources / measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study Size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time *Case-control study*—Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study*—Report numbers of outcome events or summary measures
Main Results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
DISCUSSION		
Key Results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
OTHER INFORMATION		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

** Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.*

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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STARD 2015 Checklist of Essential Items for Reporting Diagnostic Accuracy Studies

Section and Topic	No.	Item
TITLE OR ABSTRACT		
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)
ABSTRACT		
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)
INTRODUCTION		
	3	Scientific and clinical background, including the intended use and clinical role of the index test
	4	Study objectives and hypotheses
METHODS		
Study design	5	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)
Participants	6	Eligibility criteria
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)
	8	Where and when potentially eligible participants were identified (setting, location and dates)
	9	Whether participants formed a consecutive, random or convenience series
Test Methods	10a	Index test, in sufficient detail to allow replication
	10b	Reference standard, in sufficient detail to allow replication
	11	Rationale for choosing the reference standard (if alternatives exist)
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test
	13b	Whether clinical information and index test results were available to the assessors of the reference standard
Analysis	14	Methods for estimating or comparing measures of diagnostic accuracy
	15	How indeterminate index test or reference standard results were handled
	16	How missing data on the index test and reference standard were handled
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory
	18	Intended sample size and how it was determined
RESULTS		
Participants	19	Flow of participants, using a diagram
	20	Baseline demographic and clinical characteristics of participants
	21a	Distribution of severity of disease in those with the target condition
	21b	Distribution of alternative diagnoses in those without the target condition
	22	Time interval and any clinical interventions between index test and reference standard
Test Results	23	Cross tabulation of the index test results (or their distribution) by the results of the reference standard
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)
	25	Any adverse events from performing the index test or the reference standard
DISCUSSION		
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability
	27	Implications for practice, including the intended use and clinical role of the index test
OTHER INFORMATION		
	28	Registration number and name of registry
	29	Where the full study protocol can be accessed
	30	Sources of funding and other support; role of funders

This STARD list was released in 2015. The 30 items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on http://www.equator-network.org/reporting-guidelines/stard.

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CHEERS Checklist - Items to include when Reporting Economic Evaluations of Health Interventions

Section / Item	Item no.	Recommendation	Reported on page no. / line no.
TITLE AND ABSTRACT			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	
INTRODUCTION			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	
METHODS			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	
Study Perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	
	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	
Choice of model	15	Describe and give reasons for the specific type of decision analytical model used. Providing a figure to show model structure is strongly recommended.	
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	
RESULTS			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact Consolidated Health Economic Evaluation Reporting Standards – CHEERS Checklist 3 of methodological assumptions (such as discount rate, study perspective).	
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or costeffectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	
DISCUSSION			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	
OTHER INFORMATION			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	

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The ARRIVE Guidelines (Animal Research: Reporting of In Vivo Experiments)

Section / Topic	Item no.	Checklist item
TITLE AND ABSTRACT		
Title	1	Provide as accurate and concise a description of the content of the article as possible.
Abstract	2	Provide an accurate summary of the background, research objectives, including details of the species or strain of animal used, key methods, principal findings and conclusions of the study.
INTRODUCTION		
Background	3	a. Include sufficient scientific background (including relevant references to previous work) to understand the motivation and context for the study, and explain the experimental approach and rationale.
Objectives		b. Explain how and why the animal species and model being used can address the scientific objectives and, where appropriate, the study's relevance to human biology.
	4	Clearly describe the primary and any secondary objectives of the study, or specific hypotheses being tested.
METHODS		
Ethical statement	5	DIndicate the nature of the ethical review permissions, relevant licences (e.g. Animal [Scientific Procedures] Act 1986), and national or institutional guidelines for the care and use of animals, that cover the research.
Study design	6	For each experiment, give brief details of the study design including: a. The number of experimental and control groups. b. Any steps taken to minimise the effects of subjective bias when allocating animals to treatment (e.g. randomisation procedure) and when assessing results (e.g. if done, describe who was blinded and when). c. The experimental unit (e.g. a single animal, group or cage of animals). A time-line diagram or flow chart can be useful to illustrate how complex study designs were carried out.
Experimental procedures	7	For each experiment and each experimental group, including controls, provide precise details of all procedures carried out. For example: a. How (e.g. drug formulation and dose, site and route of administration, anaesthesia and analgesia used [including monitoring], surgical procedure, method of euthanasia). Provide details of any specialist equipment used, including supplier(s). b. When (e.g. time of day). c. Where (e.g. home cage, laboratory, water maze). d. Why (e.g. rationale for choice of specific anaesthetic, route of administration, drug dose used).
Experimental animals	8	a. Provide details of the animals used, including species, strain, sex, developmental stage (e.g. mean or median age plus age range) and weight (e.g. mean or median weight plus weight range). b. Provide further relevant information such as the source of animals, international strain nomenclature, genetic modification status (e.g. knock-out or transgenic), genotype, health/immune status, drug or test naïve, previous procedures, etc.
Housing and husbandry	9	Provide details of: a. Housing (type of facility e.g. specific pathogen free [SPF]; type of cage or housing; bedding material; number of cage companions; tank shape and material etc. for fish). b. Husbandry conditions (e.g. breeding programme, light/dark cycle, temperature, quality of water etc for fish, type of food, access to food and water, environmental enrichment). c. Welfare-related assessments and interventions that were carried out prior to, during, or after the experiment.
Sample size	10	a. Specify the total number of animals used in each experiment, and the number of animals in each experimental group. b. Explain how the number of animals was arrived at. Provide details of any sample size calculation used. c. Indicate the number of independent replications of each experiment, if relevant.
Allocating animals to experimental groups	11	a. Give full details of how animals were allocated to experimental groups, including randomisation or matching if done. b. Describe the order in which the animals in the different experimental groups were treated and assessed.
Experimental outcomes	12	Clearly define the primary and secondary experimental outcomes assessed (e.g. cell death, molecular markers, behavioural changes).
Statistical methods	13	a. Provide details of the statistical methods used for each analysis. b. Specify the unit of analysis for each dataset (e.g. single animal, group of animals, single neuron). c. Describe any methods used to assess whether the data met the assumptions of the statistical approach.
RESULTS		
Baseline data	14	For each experimental group, report relevant characteristics and health status of animals (e.g. weight, microbiological status, and drug or test naïve) prior to treatment or testing (this information can often be tabulated).
Numbers analysed	15	a. Report the number of animals in each group included in each analysis. Report absolute numbers (e.g. 10/20, not 50%). b. If any animals or data were not included in the analysis, explain why.
Outcomes and estimation	16	Report the results for each analysis carried out, with a measure of precision (e.g. standard error or confidence interval).
Adverse events	17	a. Give details of all important adverse events in each experimental group. b. Describe any modifications to the experimental protocols made to reduce adverse events.
DISCUSSION		
Interpretation/ scientific implications	18	a. Interpret the results, taking into account the study objectives and hypotheses, current theory and other relevant studies in the literature. b. Comment on the study limitations including any potential sources of bias, any limitations of the animal model, and the imprecision associated with the results. c. Describe any implications of your experimental methods or findings for the replacement, refinement or reduction (the 3Rs) of the use of animals in research.
Generalisability/translation	19	Comment on whether, and how, the findings of this study are likely to translate to other species or systems, including any relevance to human biology.
Funding	20	List all funding sources (including grant number) and the role of the funder(s) in the study.

The ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines were developed as part of an NC3Rs initiative to improve the design, analysis and reporting of research using animals – maximising information published and minimising unnecessary studies. The guidelines were published in the online journal PLOS Biology in June 2010 and are currently endorsed by scientific journals, major funding bodies and learned societies. More information can be found on www.nc3rs.org.uk/ARRIVE

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Revised Standards for Quality Improvement Reporting Excellence (SQUIRE 2.0)

No	Item	Guide questions / description
TITLE AND ABSTRACT		
1	Title	Indicate that the manuscript concerns an initiative to improve healthcare (broadly defined to include the quality, safety, effectiveness, patient-centeredness, timeliness, cost, efficiency, and equity of healthcare)
2	Abstract	a. Provide adequate information to aid in searching and indexing b. Summarize all key information from various sections of the text using the abstract format of the intended publication or a structured summary such as: background, local problem, methods, interventions, results, conclusions
INTRODUCTION		**WHY DID YOU START?**
3	Problem Description	Nature and significance of the local problem
4	Available knowledge	Summary of what is currently known about the problem, including relevant previous studies
5	Rationale	Informal or formal frameworks, models, concepts, and/or theories used to explain the problem, any reasons or assumptions that were used to develop the intervention(s), and reasons why the intervention(s) was expected to work
6	Specific aims	Purpose of the project and of this report
METHODS		**WHAT DID YOU DO?**
7	Context	Contextual elements considered important at the outset of introducing the intervention(s)
8	Intervention(s)	a. Description of the intervention(s) in sufficient detail that others could reproduce it b. Specifics of the team involved in the work
9	Study of the Intervention(s)	a. Approach chosen for assessing the impact of the intervention(s) b. Approach used to establish whether the observed outcomes were due to the intervention(s)
10	Measures	a. Measures chosen for studying processes and outcomes of the intervention(s), including rationale for choosing them, their operational definitions, and their validity and reliability b. Description of the approach to the ongoing assessment of contextual elements that contributed to the success, failure, efficiency, and cost c. Methods employed for assessing completeness and accuracy of data
11	Analysis	a. Qualitative and quantitative methods used to draw inferences from the data b. Methods for understanding variation within the data, including the effects of time as a variable
12	Ethical Considerations	Ethical aspects of implementing and studying the intervention(s) and how they were addressed, including, but not limited to, formal ethics review and potential conflict(s) of interest
RESULTS		**WHAT DID YOU FIND?**
13	Results	a. Initial steps of the intervention(s) and their evolution over time (e.g., time-line diagram, flow chart, or table), including modifications made to the intervention during the project b. Details of the process measures and outcome c. Contextual elements that interacted with the intervention(s) d. Observed associations between outcomes, interventions, and relevant contextual elements e. Unintended consequences such as unexpected benefits, problems, failures, or costs associated with the intervention(s). f. Details about missing data
DISCUSSION		**WHAT DOES IT MEAN?**
14	Summary	a. Key findings, including relevance to the rationale and specific aims b. Particular strengths of the project
15	Interpretation	a. Nature of the association between the intervention(s) and the outcomes b. Comparison of results with findings from other publications c. Impact of the project on people and systems d. Reasons for any differences between observed and anticipated outcomes, including the influence of context e. Costs and strategic trade-offs, including opportunity costs
16	Limitations	a. Limits to the generalizability of the work b. Factors that might have limited internal validity such as confounding, bias, or imprecision in the design, methods, measurement, or analysis
17	Conclusions	c. Efforts made to minimize and adjust for limitations a. Usefulness of the work b. Sustainability c. Potential for spread to other contexts d. Implications for practice and for further study in the field e. Suggested next steps
OTHER INFORMATION		
18	Funding	Sources of funding that supported this work. Role, if any, of the funding organization in the design, implementation, interpretation, and reporting

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section / Topic	Item no.	Description
ADMINISTRATIVE INFORMATION		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding	4	Sources and types of financial, material, and other support
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
INTRODUCTION		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b	Explanation for choice of comparators
Objectives	7	Specific objectives or hypotheses
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)
METHODS: PARTICIPANTS, INTERVENTIONS, AND OUTCOMES		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size
METHODS: ASSIGNMENT OF INTERVENTIONS (FOR CONTROLLED TRIALS)		
Allocation:		
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial

METHODS: DATA COLLECTION, MANAGEMENT, AND ANALYSIS		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
METHODS: MONITORING		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
ETHICS AND DISSEMINATION		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
APPENDICES		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

**It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.*

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The complete checklists and full guidelines are available at http://equator-network.org.

CONSORT 2010 Checklist of Information to include when Reporting a Randomised Trial*

Section / Topic	Item no.	Checklist item	Reported on page no.
TITLE AND ABSTRACT			
	1a	Identification as a randomised trial in the title	_____
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	_____
INTRODUCTION			
Background and objectives	2a	Scientific background and explanation of rationale	_____
	2b	Specific objectives or hypotheses	_____
METHODS			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	_____
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	_____
Participants	4a	Eligibility criteria for participants	_____
	4b	Settings and locations where the data were collected	_____
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	_____
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	_____
	6b	Any changes to trial outcomes after the trial commenced, with reasons	_____
Sample size	7a	How sample size was determined	_____
	7b	When applicable, explanation of any interim analyses and stopping guidelines	_____
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	_____
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	_____
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	_____
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	_____
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	_____
	11b	If relevant, description of the similarity of interventions	_____
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	_____
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	_____
RESULTS			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	_____
	13b	For each group, losses and exclusions after randomisation, together with reasons	_____
Recruitment	14a	Dates defining the periods of recruitment and follow-up	_____
	14b	Why the trial ended or was stopped	_____
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	_____
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	_____
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	_____
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	_____
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	_____
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	_____
DISCUSSION			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	_____
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	_____
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	_____
OTHER INFORMATION			
Registration	23	Registration number and name of trial registry	_____
Protocol	24	Where the full trial protocol can be accessed, if available	_____
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	_____

** We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.*

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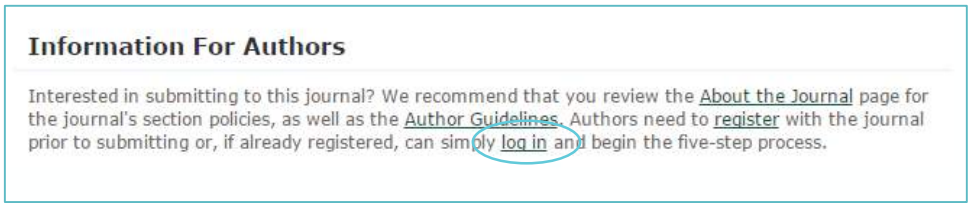
PJP Online Journal System

User Guide for Authors

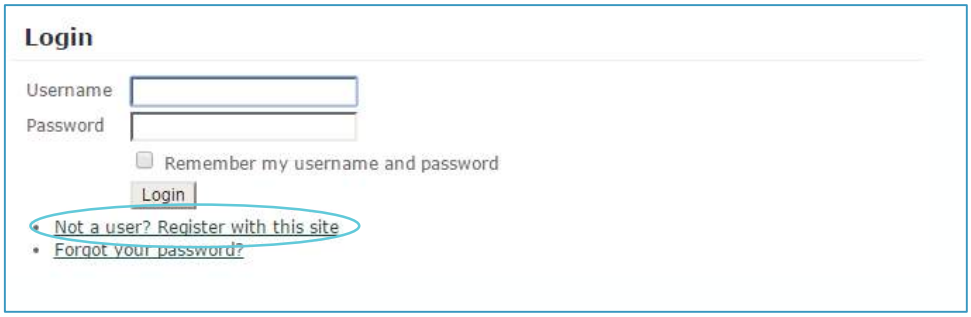
Getting Started

- From the PJP website (http://www.philippinejournalofpathology.org), navigate to 'For Authors'. (add screenshot of PJP landing page, circle 'for authors' on right column).

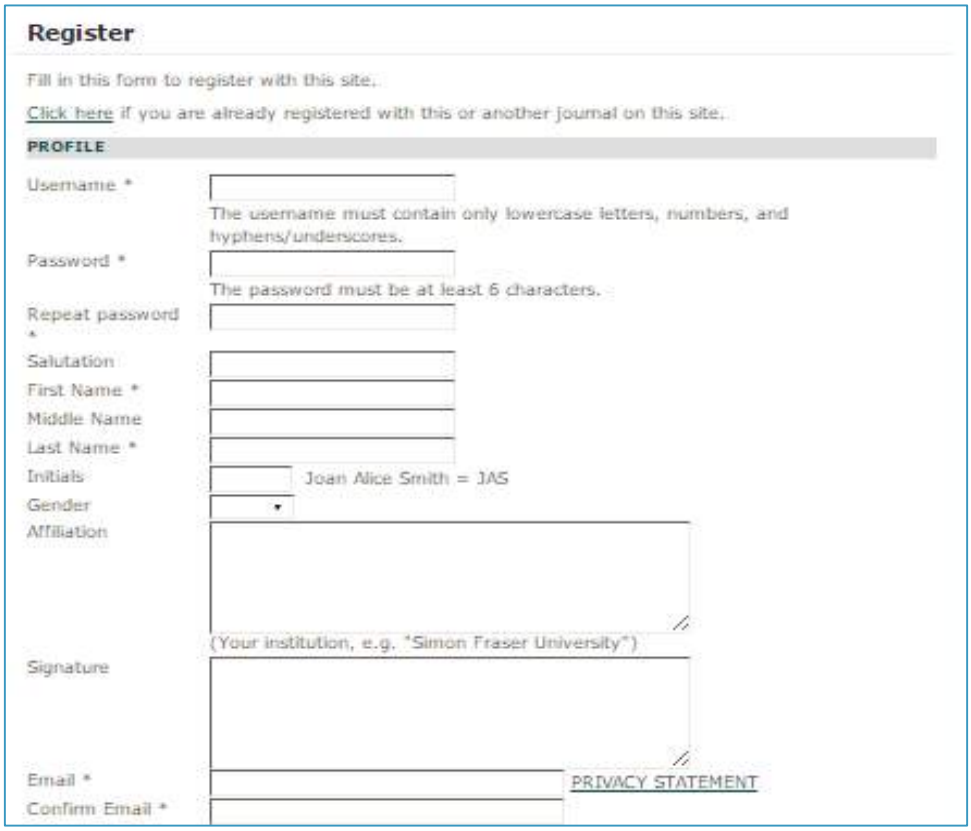
Select 'FOR AUTHORS'.

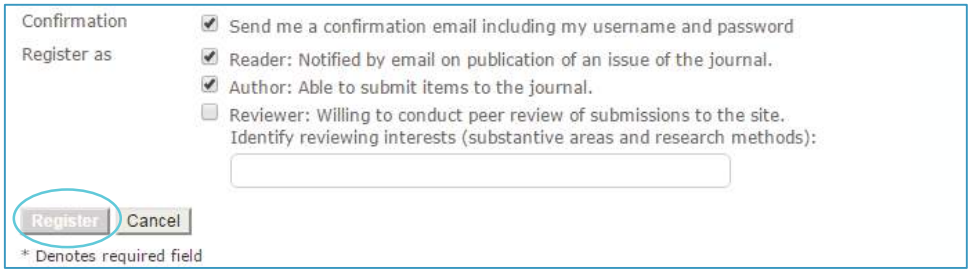


- Log in
- New user:
  - If you are a new user of the PJP website, please register by clicking the link 'Not a user, Register with this site'.

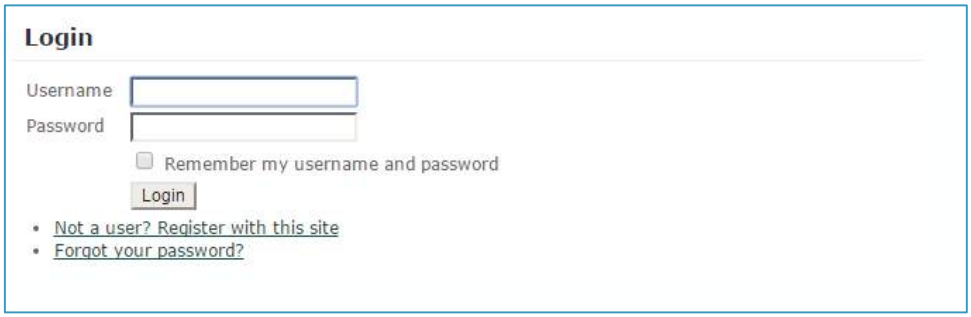


  - Complete the online form then select 'Register'. A confirmation email with your username and password will be sent to your email address.





- Existing user:
  - Log in to your OJS account using the username and password from original registration.
  - If you have forgotten your log in details, please click the 'Forgot the password?' and an email will be sent to your registered email address.

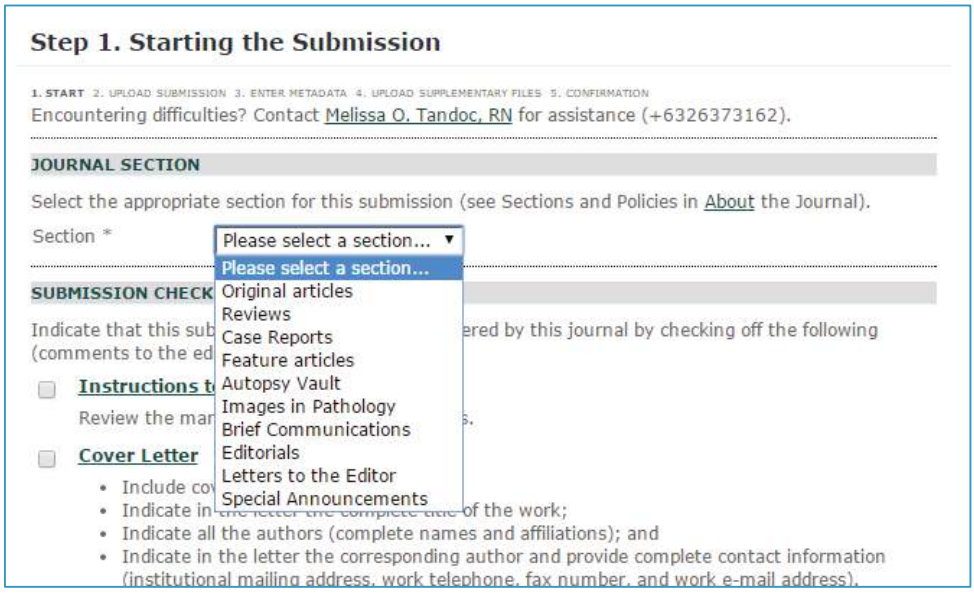


The Submission Process

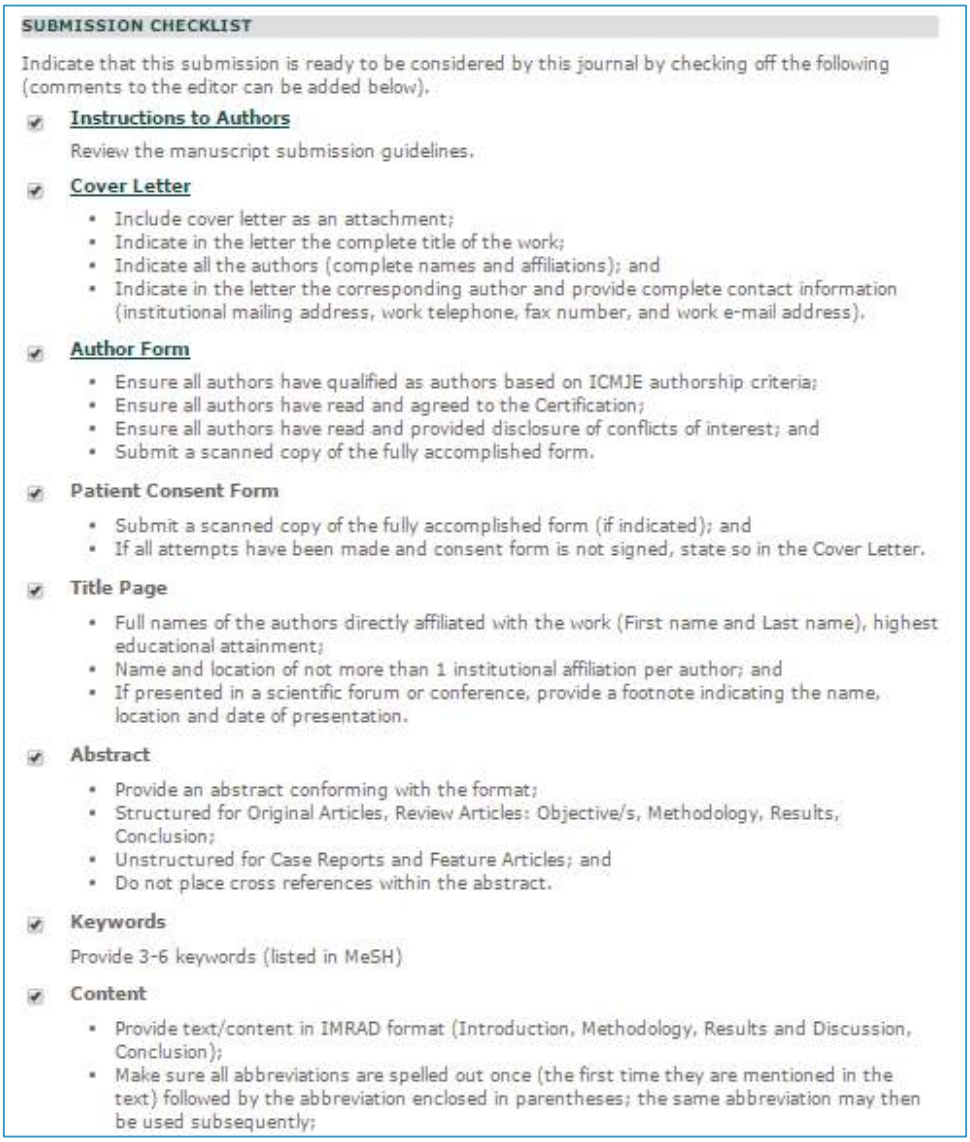
- To start the submission process, click 'New Submission'

Step 1: Starting the submission

- From the drop-down menu, please select the most appropriate section to describe your submission article type. If you are not sure what section to select, click 'About' to find out more information.



- Please ensure the items listed in the checklist are ready then tick each box.



SUBMISSION CHECKLIST

Indicate that this submission is ready to be considered by this journal by checking off the following (comments to the editor can be added below).

☑ **Instructions to Authors**

Review the manuscript submission guidelines.

☑ **Cover Letter**

- Include cover letter as an attachment;
- Indicate in the letter the complete title of the work;
- Indicate all the authors (complete names and affiliations); and
- Indicate in the letter the corresponding author and provide complete contact information (institutional mailing address, work telephone, fax number, and work e-mail address).

☑ **Author Form**

- Ensure all authors have qualified as authors based on ICMJE authorship criteria;
- Ensure all authors have read and agreed to the Certification;
- Ensure all authors have read and provided disclosure of conflicts of interest; and
- Submit a scanned copy of the fully accomplished form.

☑ **Patient Consent Form**

- Submit a scanned copy of the fully accomplished form (if indicated); and
- If all attempts have been made and consent form is not signed, state so in the Cover Letter.

☑ **Title Page**

- Full names of the authors directly affiliated with the work (First name and Last name), highest educational attainment;
- Name and location of not more than 1 institutional affiliation per author; and
- If presented in a scientific forum or conference, provide a footnote indicating the name, location and date of presentation.

☑ **Abstract**

- Provide an abstract conforming with the format;
- Structured for Original Articles, Review Articles: Objective/s, Methodology, Results, Conclusion;
- Unstructured for Case Reports and Feature Articles; and
- Do not place cross references within the abstract.

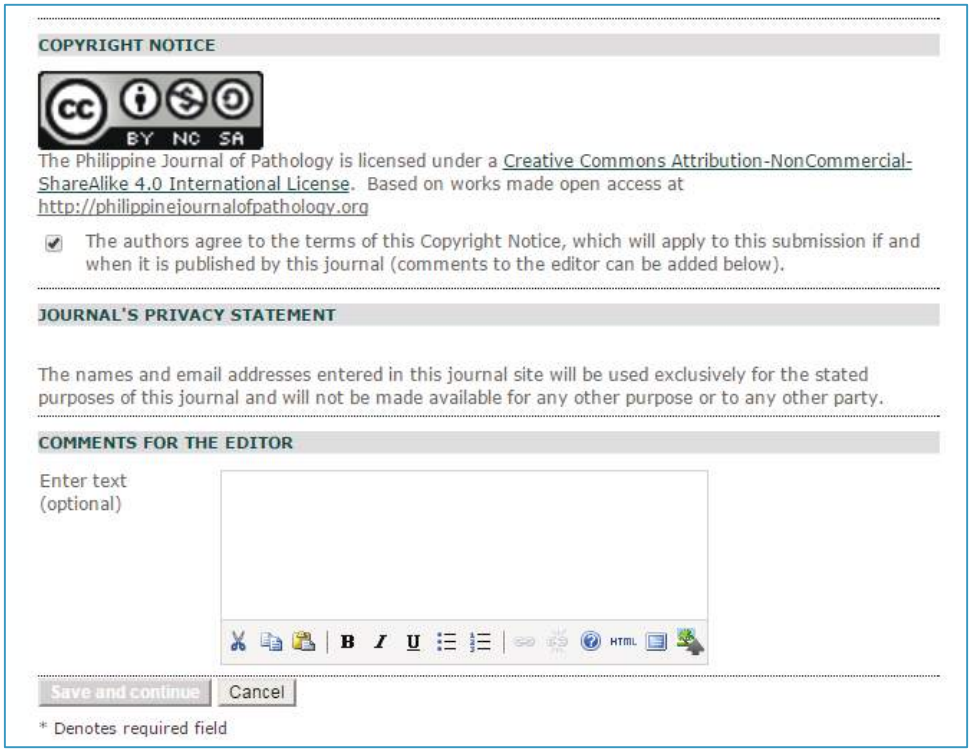
☑ **Keywords**

Provide 3-6 keywords (listed in MeSH)

☑ **Content**

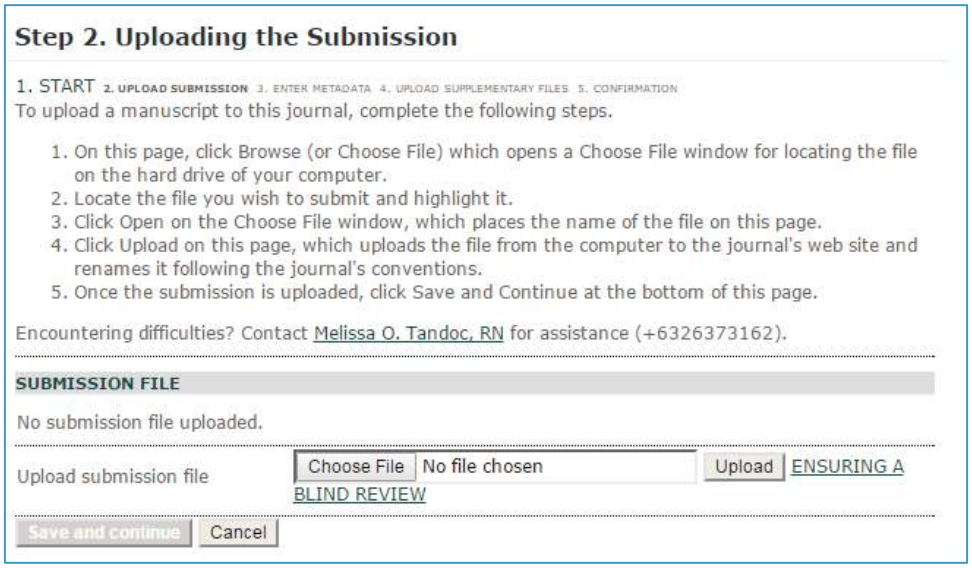
- Provide text/content in IMRAD format (Introduction, Methodology, Results and Discussion, Conclusion);
- Make sure all abbreviations are spelled out once (the first time they are mentioned in the text) followed by the abbreviation enclosed in parentheses; the same abbreviation may then be used subsequently;

- Read the 'Copyright Notice' and add comments to the editor (optional). Select 'Save and continue'.



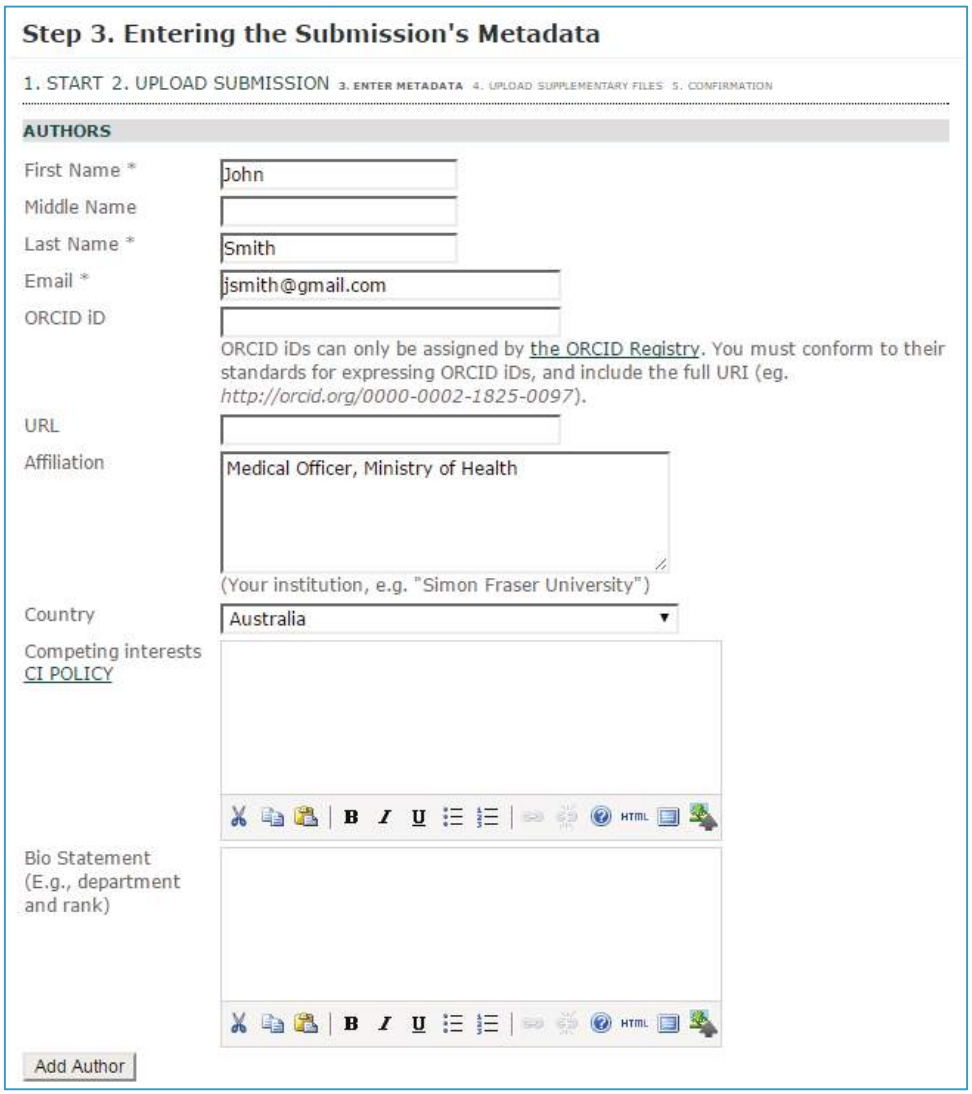
Step 2: Uploading the Submission

- Please follow the instructions on this page to upload your file, then select 'Save and continue'. This is where you upload the **manuscript only**. (You will be asked to upload other required documents at Step 4.

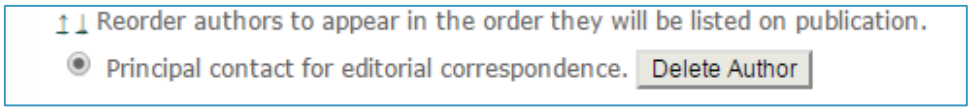


Step 3: Entering the Submission's Metadata

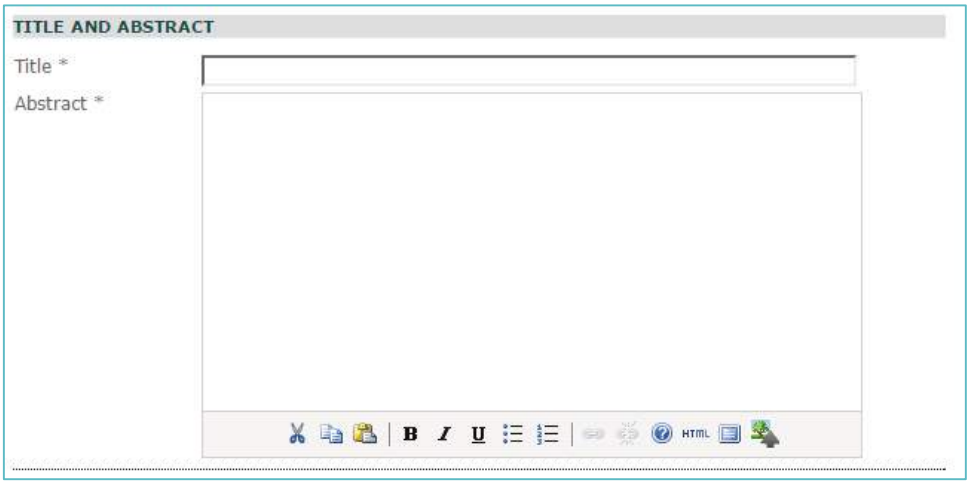
- Complete author(s)'s information as much as you can. Fields marked with * are mandatory. If you have more than one author for your submission, click 'Add author' for each of these.

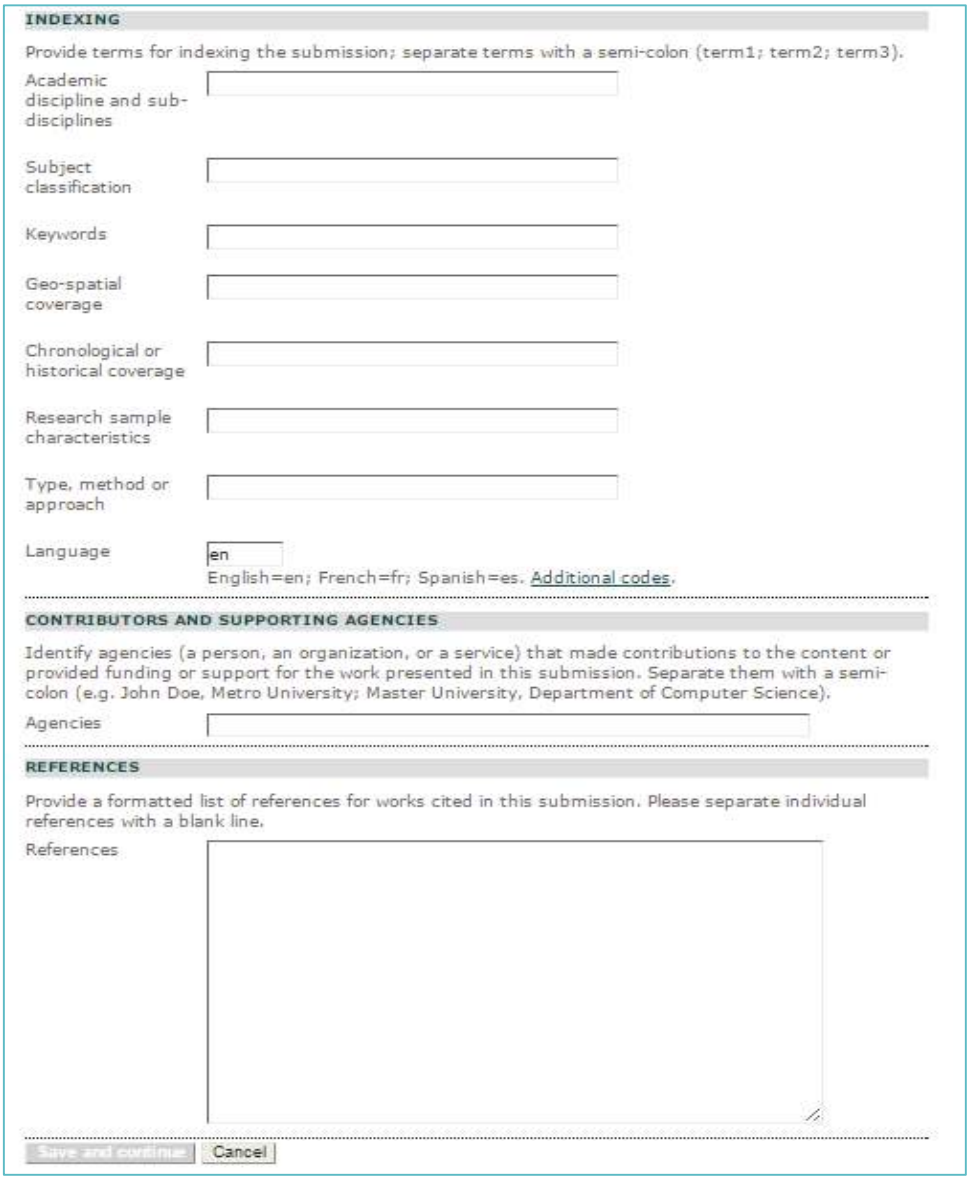


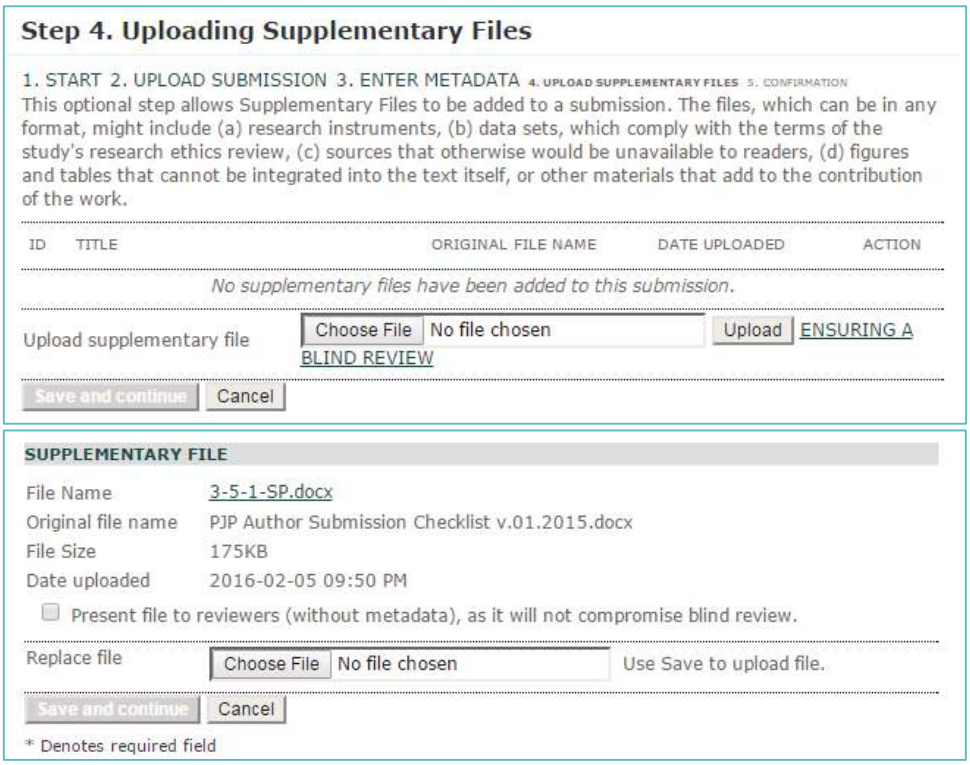
- Please note the system will automatically select the first-recorded author as the principal contact for editorial correspondence. If you want to change this, choose the following option listed at the bottom of the author details for the author you want to be the principal contact.



- Complete 'Title', 'Abstract', 'Indexing' and 'Supporting Agencies' of your submission. Select 'Save and continue'. These can be pasted from a word document.







- Once all files are uploaded, if you need to you can edit or delete them by clicking the links. To continue to next step, select 'Save and continue'.

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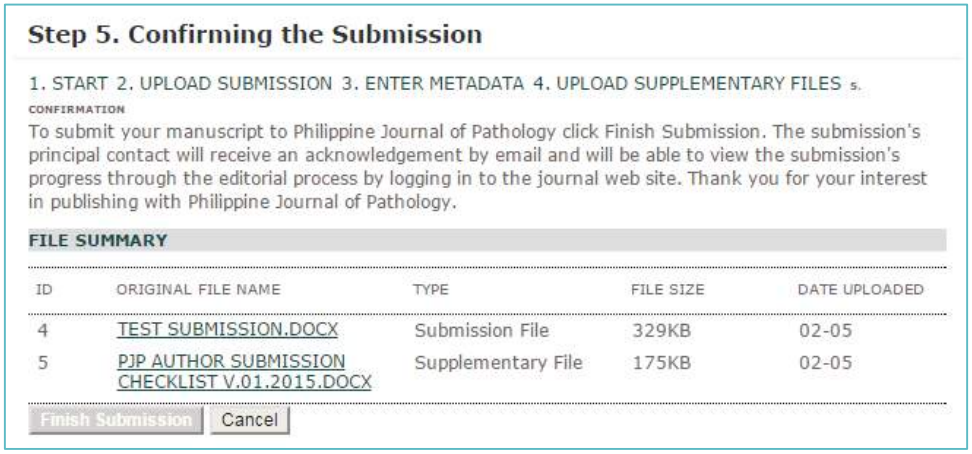

Step 5. Confirming the Submission

1. START 2. UPLOAD SUBMISSION 3. ENTER METADATA 4. UPLOAD SUPPLEMENTARY FILES 5. CONFIRMATION

To submit your manuscript to Philippine Journal of Pathology click Finish Submission. The submission's principal contact will receive an acknowledgement by email and will be able to view the submission's progress through the editorial process by logging in to the journal web site. Thank you for your interest in publishing with Philippine Journal of Pathology.

FILE SUMMARY

ID	ORIGINAL FILE NAME	TYPE	FILE SIZE	DATE UPLOADED
4	TEST SUBMISSION.DOCX	Submission File	329KB	02-05
5	PJP AUTHOR SUBMISSION CHECKLIST V.01.2015.DOCX	Supplementary File	175KB	02-05

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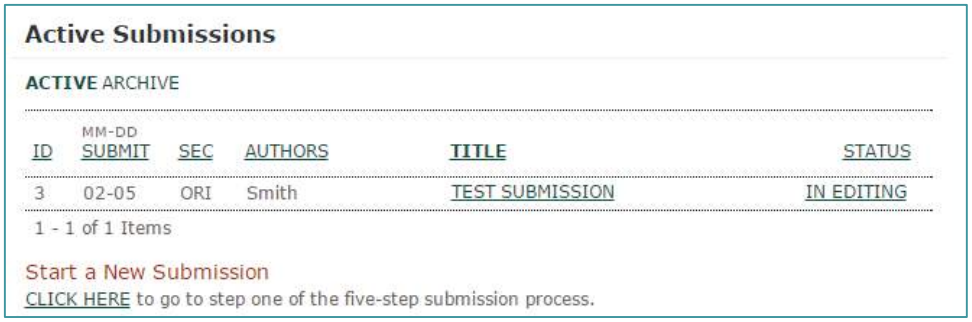
Status of Submission

- During the review and editing process, the principal contact can log in to the PJP website to check the status of the submission. Follow the log in instructions on Page (?) and then click the 'Active' tab.



Active Submissions

ACTIVE ARCHIVE

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3	02-05	ORI	Smith	TEST SUBMISSION	IN EDITING

1 - 1 of 1 Items

Start a New Submission
CLICK HERE to go to step one of the five-step submission process.

- You will receive an email from the Editor-in-Chief after the peer review process which will indicate the outcome of the review and provide the reviewer's comments.

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> Your manuscript "xxxxxx" submitted to Philippine Journal of Pathology has undergone peer review. The manuscript has been accepted subject to major / minor revisions.
>
> Please find attached the comments from the peer reviewers. Please take the following actions:
> 1. Review the manuscript according to the reviewers' comments using the track changes facility in Word.
> 2. Provide a response to each of the reviewers' comments in a separate Word document.
> 3. Upload both the revised manuscript and the response to the reviewers' comments.
>
> The due date for these revisions is Friday, xx month. If you have any queries regarding this please contact me.
>
> Thank you and kind regards,
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- Please make the required changes to manuscript and in a **separate** file provide responses to each of the reviewer's comments.
- These can then be uploaded onto the system.
    - Login (see instructions on Page (?))
    - Click 'Active' tab.
    - Click on your submission listed below 'TITLE'.
    - Select the 'Review' tab.
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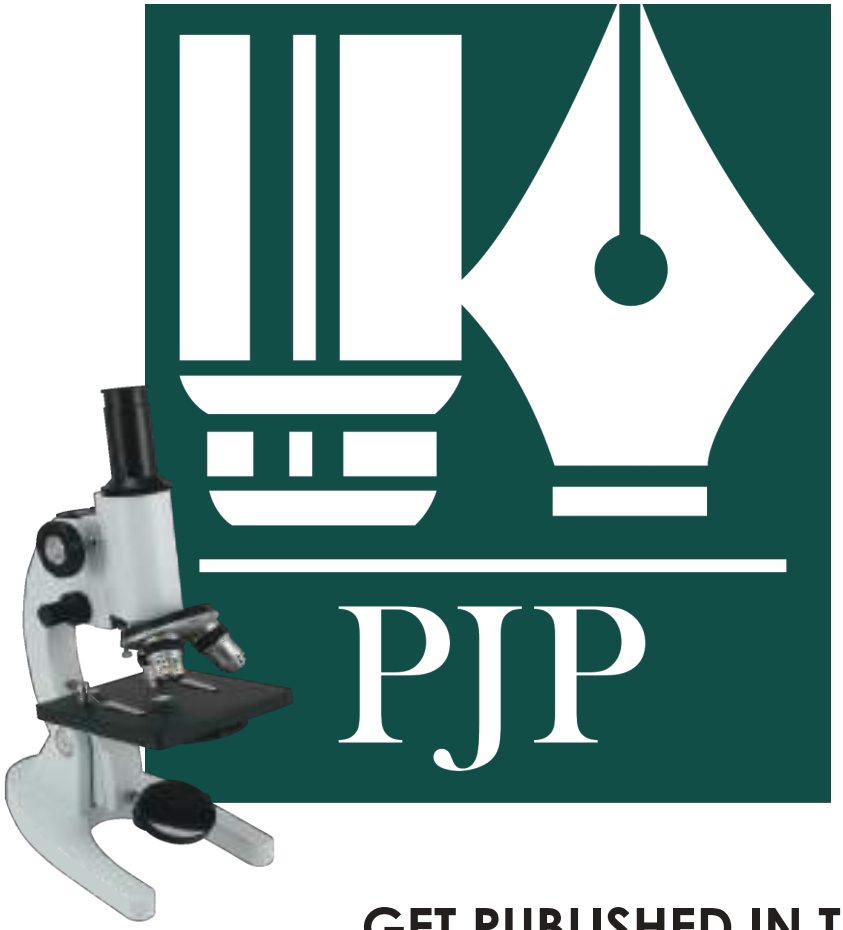
    - Once you have uploaded your files, you can view them at the 'Author's Version' section.



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