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Evidence-Based Pathology

Pathology in the era of “Personalized Medicine": The need to learn how to integrate multivariate immunohistochemical and “omics” data with clinicopathologic information in a clinically relevant way”

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ABSTRACT

“Personalized medicine” has been proposed as a new paradigm for patient care that, based on the integration of genomics and other “omics” data with clinical and other multidisciplinary information, promises early disease detection, improved outcomes and reduced side effects to therapies. Pathologists have become important participants in this new approach as the guardians of tissues and experts in the performance of molecular and other laboratory tests. Large amounts of new laboratory data in multiple neoplasms and other entities are being reported but there has been limited discussion about how best to evaluate the clinical significance of this information and how to integrate it into currently available diagnostic and therapeutic modalities. This article introduces a variety of epistemological problems presented by the “personalized medicine” paradigm and briefly discusses various topics that will be evaluated in further detail in future articles of this new series on Evidence-Based Pathology.

“Personalized medicine” has been proposed as a new paradigm for patient care that, based on the integration of genomics and other “omics” data with clinical and other multidisciplinary information, promises early disease detection, improved outcomes and reduced side effects to therapies [1-5]. Risk assessments models are being developed to facilitate accurate diagnoses and select therapeutic strategies that are specifically designed to optimize the management of individual patients [6-15]. Ironically, although pathology has been regarded as an increasingly obsolete specialty being rapidly outdated by advances in automated digital imaging, artificial intelligence and other technologies, the specialty is at the center of this new era as the guardian of tissues and other biologic samples [16,17]. Indeed, “personalized medicine” relies heavily on laboratory data including histopathologic diagnosis, immunohistochemical findings, genomics, proteomics and other test results performed on various specimens [18-20]. These studies generate reams of new data and present challenges about how to best apply this ‘evidence’ to individual patients rather groups of individuals [9,15,21].

The “personalized medicine” era raises questions about who the “integrator” of these data will be and whether pathologists have been properly trained to understand how multivariate data and often conflicting or uncertain evidence can be integrated to provide the most helpful information to individual patients while not exceeding sustainable health care costs. This article introduces several epistemological issues relevant to these questions. We anticipate that each of these questions and additional topics will be explored in future articles in this new series on evidence-based pathology practice.

1. How can pathologists evaluate the quality of published results? Evidence levels

Scientific questions can be investigated using various study designs that have been explored in the evidence-based pathology literature [22-27]. It is beyond the scope of this article to discuss this topic in detail, but it is discussed in multiple resources in books, articles and websites. For example, the Centre for Evidence Based Medicine at Oxford University in the U.K. offers excellent educational materials about study designs [28]. Table 1 shows a simplified summary of study designs, including observational and experimental studies and systematic reviews. Observational studies are most often used in pathology to explore the features of unusual conditions, describe with the aid of statistical methods the characteristics of certain populations of patients or

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Table 1
Types of study design.

Observational designs
Exploratory studies: report unusual or unknown diseases
Case reports
Case series: describe characteristics of diseases and evaluate the findings with statistics
Case-control series: commonly used in pathology studies
Cross-sectional series: describe the frequency and characteristics of a disease at a particular point in time
Cohort studies: longitudinal observations over time
Experimental designs
Randomized clinical studies: usually not suitable for questions explored in pathology
Systematic reviews: comprehensive review of available evidence evaluating available information qualitatively or quantitatively using meta-analysis

test various hypothesis. Case reports and case series can produce valuable information to understand clinico-pathologic entities and this evidence can be used to design future randomized clinical trials and/or influence clinical practice in situations when is not feasible to perform these trials. However, the information provided by case reports and case series is subject to strong publication bias toward positive results. Randomized controlled trials are experimental studies where allocation to treatment and control groups are done randomly, to reduce selection bias, publication bias and other potential shortcoming of study design.

Various scales of evidence level have been proposed to inform readers of scientific publications about the "quality" of information yielded by various study designs [29]. The various proposed scales of levels of evidence can be oversimplified as 1 through 5, with level 1 providing the highest-level quality of information. Level 1 evidence is provided by randomized clinical trials, level 2 evidence is provided by systematic reviews of homogeneous cohort studies. Level 3 or 4 evidence is provided by case series or control studies, depending on their study designs. Level 5 evidence is provided by expert opinion offered without generation of data or critical appraisal of evidence from literature. As it is not feasible to conduct randomized clinical trials in pathology, this scale would imply that all pathology studies are relatively "low quality", although our specialty has provided a wealth of valuable medical knowledge. We have proposed the scale of evidence levels for publications in pathology and laboratory medicine shown in Table 2, that is more appropriate to gauge the quality of information gendered by pathologists and stimulate best practices [30].

Table 2
Scale of evidence levels proposed for pathology and laboratory medicine[a].

Level 1: Case-control studies with external validation of results using prospective data from other institutions
Meta-analysis of level 2 studies
Expert recommendations based on level 2 or 3 studies
Level 2: Case-control studies with external validation of results using prospective data from the same Institution
Meta-analysis of level 3 studies
Expert recommendations based on a systematic review of literature but without meta-analysis
Level 3: Case-control studies with external validation of results using retrospective data from the same Institution
Level 4: Case-control studies
Level 5: Case reports
Case series without controls

[a] This scale was proposed by Marchevsky A and Wick to evaluate the quality of observational studies in pathology publications [30].

2. How should old and new information be evaluated in a manner that is clinically applicable to individual patients rather than obtaining significant "p values" for retrospective groups of patients?

Many pathologists might argue that our specialty is "evidence-based" as we continue to collect detailed and "objective" information from specimens using an increasing variety of advanced laboratory techniques. In general, new findings are accepted only after results are shown to be "statistically significant", and new findings are interpreted as "clinically significant" if they are significantly associated (p value ≥ 0.5) with overall survival or other prognostic endpoints and/or response to therapies [25-27,31]. However, many of these observational studies in anatomic pathology are retrospective, include a relatively small number of patients, and/or are not validated in other patient cohorts prior to publication, yielding level 3 or 4 evidence. Also, in anatomic pathology "objective" findings are often based on subjective interpretations of microscopic features. Even "instrument-based" laboratory tests such as immunohistochemistry and DNA analysis require the adoption of multiple technical/ procedural details that are selected based on experience and personal judgement. Thus, regarding biologic samples, the so-called "best available evidence" is frequently obtained from observational studies, somewhat incomplete and/or subjective data, small number of observations and variable methodologies and interpreted with the help of opinion experts [25].

Evidence-based medicine and its derivative evidence-based pathology have been proposed as a way to analyze and interpret medical and laboratory data so as to provide maximum benefit to individual patients [25,27,31,32]. Yet, the limitations of information obtained with observational studies is seldom discussed in the pathology literature and is periodically used to suggest more aggressive therapeutic modalities based on groups of patients that exhibit worse prognosis in those studies. For example, spread though airways (STAS) has been shown to be associated with prognosis in several observational studies of patients with lung adenocarcinoma and other neoplasms, although some investigators have raised questions whether this finding results from artifactually detached loose tumor fragments [32-35]. In patients with lung adenocarcinoma, the association with prognosis is statistically significant in patients undergoing sublobar resections, suggesting that STAS needs to be identified preoperatively or intraoperatively in order to stratify which patients would putatively benefit from lobectomy. However, is there enough evidence in literature to introduce this hypothesis into current clinical practice? We investigated the presence of STAS in frozen sections of our lung adenocarcinoma patients, were able to detect their presence in some but not all patients and concluded that there was insufficient evidence to warrant recommending the performance of lobectomy to our thoracic surgeons based on this finding [32]. Expert pathologists reading this study opined that this approach is too conservative, that STAS can be detected in a substantial number of frozen sections and that as their presence has been shown to be associated with prognosis in several observational studies, thoracic surgeons should be informed about their presence so that they can perform a more extensive resection (personal communication). In contrast, evidence-based pathology proponents would advocate classifying this type of evidence as level 3 or 4 and using it only as a hypothesis to be tested on a randomized clinical trial before a recommendation into routine clinical practice is issued, illustrating the difference between this approach and "expert opinion".

These problems raise the fundamental question of what is a pathologist to do in the presence of incomplete and somewhat uncertain evidence? Evidence-based pathology advocates the estimation of probabilities, odds, positive/negative predictive values, and likelihood ratios to express the likelihood of individual events [25]. The NCCN and other evidence-based guidelines advocate the use of randomized clinical trials to determine the utility of new therapeutic modalities [24]. It is beyond the scope of this article to discuss the advantages and

disadvantages of these metrics that are widely used in laboratory medicine but not in anatomic or molecular pathology. In general, anatomic and molecular pathology data are often correlated with prognosis or "prediction" of therapy response and results are being read as clinically significant, particularly if reproduced in several observational studies and although interesting correlations with significant "p" values do not necessarily indicate that the information is clinically relevant, as discussed in the next section of this article [10].

3. Can the results of prognostic studies obtained from retrospective groups of cases be accurately used to estimate the clinical course and/or response to treatment in patients who were not included in the study?

The topic of "prognosis" has been evaluated much more extensively in oncology and other medical specialties than in pathology [8,9,22,36,37]. In pathology studies, the usual methodology involves correlation of overall survival, and occasionally disease-specific survival with various histopathology and laboratory data. Although extreme care is usually expended to obtain precise pathology and laboratory data, the dependent variable "survival" is often not normalized by other variables such as disease specific survival, age, stage, treatment and other variables that can influence the results considerably. Importantly, this methodology can only provide level 3 or 4 evidence that does not necessarily predict the outcome in future patient cohorts and cannot predict the prognosis or response to treatment in future individuals [15]. For example, multiple studies have shown that lung adenocarcinoma (LADC) exhibiting micropapillary (MIP) growth features are associated with a worse prognosis than those with other histopathologic patterns [10,38-40]. One of the most recent studies showed in a retrospective observational study of 87 cases, that a newly recognized filigree pattern of MIP LADC was associated with worse recurrence free probability and lung cancer-specific survival than other histologic subtypes and concluded that this finding is clinically significant [10]. Although this is certainly an excellent observational study, should this level 3 evidence be used to inform patients that they have a particularly aggressive form of lung cancer and recommend to oncologists that they should treat the patients more aggressively? A recent comprehensive review by Cao et al. concluded that "a complete lobectomy may be more suitable than limited resection for micropapillary adenocarcinoma because of the low sensitivity of intraoperative frozen sections and the high risk of lymph node metastasis. MIP benefits more from adjuvant therapy" [40]. The study is an example of "jumping to conclusions based on low level evidence" as it of does not discuss in detail whether MIP can be reliably diagnosed by different pathologists and does not quote the results of randomized clinical trials supporting the therapeutic recommendations. Indeed, another recent comprehensive review by C Monroig-Bosque et al. looked at the same literature and highlighted "the fact that there have been no studies validating the diagnostic/morphologic criteria that should be used to achieve an accurate diagnosis of micropapillary lung adenocarcinoma" [38]. The study recognized "that a micropapillary carcinoma component is associated with poor prognosis in patients with lung adenocarcinoma" but did not offer therapeutic recommendations based on available evidence. Instead, it suggested the more modest conclusion that the recognition of this type of tumors "present the potential for new research opportunities, particularly molecular studies aimed at determining targeted treatment options".

4. Which methods should be used to estimate the clinical course and/or response to treatment of future patients? The development of prognostic and predictive models based on multivariate data and evaluation of their accuracy using independent prospective datasets

The statistical tests most commonly utilized in pathology studies to evaluate prognosis and prediction of response to therapy are the Kaplan-Meier method and Cox-regression analysis [41-43]. The Kaplan-Meier method compares whether survival curves from different populations are significantly different from each other. Cox-regression analysis evaluates whether various parameters independently correlate with prognosis; the results can be used to select predictors that could be useful to formulate multivariate prognostic models. To estimate the probability that a specific event, such as recurrence or death will occur in the future there is a need to use multivariate "prognostic models", "risk scores", "prediction rules" or other tools that combine multiple predictors, usually by assigning relative weights to each predictor to obtain a risk or probability estimate [15,21,44].

A group of prediction model researchers, methodologists, various health care professionals and editors from Annals of Internal Medicine, British Medical Journal, Journal of Clinical Epidemiology and PLoS Medicine convened a meeting in 2011 to develop the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) statement in 2015 [9,45,46]. This statement discussed the similarities and differences between diagnostic and prognostic prediction models, various types of prediction models, and provides checklists of items to include when reporting a study developing or validating a multivariate prediction model for diagnosis or prognosis. Other examples of reporting recommendations include the REporting recommendations for tumor MARKer prognostic studies (REMARK), Genetic Risk Prediction Studies (GRIPS) and others [47,48]. To our knowledge, there has been limited interest at adopting these methodologies for the reporting of prognostic and predictive estimates in the pathology literature.

In addition to risk scores, nomograms and "prediction rules", statistical methods such as logistic regression, neural networks (so-called "deep learning"), Bayesian belief networks, Monte Carlo simulations and other statistical methods can be used to develop multivariate prognostic and predictive models that provide the probabilities or odds that particular events will develop in a patient [25]. Prediction models based on these methods are generally categorized as model development, model validation with or without updating or a combination of both [12-14,37,49]. It is beyond the scope of this introductory paper to describe the technical details of these methods and guidelines in detail. However, we encourage readers to consider the quality level of available evidence before opining that one of their patients with a particular tumor subtype or molecular phenotype has a "poor" or "good" prognosis". Relatedly, if prognostic or predictive information could be obtained from the results of several retrospective case-control studies, why would drug companies, oncologists and other physicians be required by the Food and Drug Administration and the National Comprehensive Cancer Network to perform very time consuming and expensive randomized clinical trials before a new treatment is approved and adopted into widely used clinical practice guidelines [24].

5. Should the accuracy of test results in anatomic pathology be evaluated and informed to patients and their clinicians?

Laboratory medicine has a long tradition of evaluating the accuracy and potential clinical applicability of new tests based on their range of normal values, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and/or likelihood ratios [41-43,50]. These metrics require information regarding the incidence of true and false positive and negative test results in selected patient populations and are used to inform physicians about their applicability to clinical problems. The College of American Pathologists requires validation of some of these metrics before new lab tests can be offered to patients [51].

In contrast, test results generated in the anatomic pathology laboratory, including diagnoses, and reporting of staging information, predictive markers and other information that are widely used in clinical practice have, for the most part, not been subjected to these

metrics, although there are many studies documenting variable incidences of diagnostic errors and considerable interobserver variability even amongst experts for the diagnosis of certain clinico-pathologic entities and the interpretation of immunostains [52-56]. Interestingly, although the results of cytologic tests are often considered as less accurate than biopsy results, proficiency testing is required in gynecologic cytology, and cytology laboratories monitor and report false negative and false positive rates and other quality assurance data for breast, thyroid and other fine needle aspiration specimens [57-59]. Biopsy diagnoses and interpretation of immunostains that require physicians' interpretative skills and/or the integration of histopathologic findings with imaging and clinical data are test results that can be impacted by interobserver variability, ambiguous terminology and other issues but are not subject to proficiency testing requirements in the U.S.

To our knowledge, the effect of this variability on multivariate personalized medicine models has not been evaluated.

6. Does every new test really provide incremental diagnostic or prognostic value in routine pathology practice?

New immunohistochemical and other laboratory tests are being reported in the pathology literature at a rapid pace. Their sensitivity and specificity are often compared with those of older/ more established tests, but these comparisons do not necessarily provide information regarding the incremental value of the new tests to increase diagnostic or predictive accuracy. For example, Ordonez, a pathologists with extensive experience in the use of immunohistochemistry for the diagnosis of mesothelioma suggested in 2005 that D2-40 was one of the most useful antibodies, as it is was positive in 86% of epithelioid mesotheliomas [60]. However, the antibody was negative in most sarcomatoid mesotheliomas and the study did not propose an optimal combination of antibodies that would diagnose with the highest sensitivity and specificity the different subtypes of mesothelioma. A recent meta-analysis evaluating the utility of D2-40 for the diagnosis of mesothelioma concluded that it needs to be combined with other antibodies for this diagnosis [23]. Practicing pathologists are still left with the problem of choosing the antibodies that would work best in their laboratories to diagnose mesotheliomas and to select the number of antibodies that should be used in a diagnostic panel. Intuitively, they may decide that “more is better” and use as many relevant antibodies as possible, to make the diagnosis as accurate as possible. However, we have shown that panels with only 2 antibodies could yield significantly better results than panels composed of 15 immunohistochemical tests for the distinction between epithelioid mesothelioma and lung adenocarcinoma [61].

7. What is the value to a current patient that pathologists incorporate all new histopathologic classifications and test results reported in recent research studies?

Although one of the roles of academic pathologists is to advance knowledge by proposing more detailed classifications and developing new laboratory tests, both academic and practicing pathologists have an obligation to patients and to society to question whether and how much of the seemingly endless new testing should be performed and reported in routine practice before its clinical applicability has been clearly adequately demonstrated. While performing and reporting an increasing number of details (e.g. results of a list of multiple low sensitivity and low specificity immunohistochemical stains or the identification of molecular variants of undetermined clinical significance) increases the complexity of pathology reports, laboratory resources, and health care costs, this practice might be of minimal value in the diagnosis, prognosis, and clinical management of contemporary patients. Despite the paramount importance of these issues, to our knowledge they have received relatively little attention in the recent pathology literature.

8. Are pathologists still the “doctors-doctors”? What role should pathologists assume in developing test utilization guidelines for pathology practice?

Historically, pathologists have been considered as the “doctors'-doctors” providing the “last word” about diagnoses and the effects of treatment by performing autopsies and assisting practitioners with interpretation of laboratory test results [62]. However, the number of autopsies being performed has declined considerably and medicine has become too complex for pathology generalists to provide all the advice required about the interpretation of lab tests. Subspecialization has become increasingly prevalent in multiple clinical disciplines, including pathology and personalized medicine protocols are being developed by multidisciplinary teams [19]. If pathologists are to maximize their contributions to patients and their clinicians in the era of personalized medicine, further consideration and focused instruction regarding these and related issues by current and future generations of pathologists are warranted.

Declaration of competing interest

The paper has not been submitted to another journal for publication. None of the authors have competing interests to declare.

References

[1] Aftimos PG, Barthelemy P, Awada A. Molecular biology in medical oncology: diagnosis, prognosis, and precision medicine. Discov Med 2014;17:81–91.
[2] Blau A, Brown A, Mahanta L, Amr SS. The translational genomics core at partners personalized medicine: facilitating the transition of research towards personalized medicine. J Pers Med 2016;6.
[3] Dolan SM. Personalized genomic medicine and prenatal genetic testing. JAMA 2014;312:1203–5.
[4] Dunnenberger HM, Khandekar JD. Value of personalized medicine. JAMA 2016;315:612–3.
[5] Jameson JL, Longo DL. Precision medicine—personalized, problematic, and promising. N Engl J Med 2015;372:2229–34.
[6] Seyedin SN, Mitchell DL, Mott SL, Russo JK, Tracy CR, Snow AN, et al. Is more always better? An assessment of the impact of lymph node yield on outcome for clinically localized prostate cancer with low/intermediate risk pathology (pT2-3a/pN0) managed with prostatectomy alone. Pathol Oncol Res 2019;25:209–15.
[7] Perrot A, Lauwers-Cances V, Tournay E, Hulin C, Chretien ML, Royer B, et al. Development and validation of a cytogenetic prognostic index predicting survival in multiple myeloma. J Clin Oncol 2019;37:1657–65.
[8] Damen J, Hooft L. The increasing need for systematic reviews of prognosis studies: strategies to facilitate review production and improve quality of primary research. Diagn Progn Res 2019;3:2.
[9] Heus P, Damen J, Pajouheshnia R, Scholten R, Reitsma JB, Collins GS, et al. Uniformity in measuring adherence to reporting guidelines: the example of TRIPOD for assessing completeness of reporting of prediction model studies. BMJ Open 2019;9:e025611.
[10] Emoto K, Eguchi T, Tan KS, Takahashi Y, Aly RG, Rekhtman N, et al. Expansion of the concept of micropapillary adenocarcinoma to include a newly recognized filigree pattern as well as the classical pattern based on 1468 stage I lung adenocarcinomas. J Thorac Oncol 2019;14(11):1948–61.
[11] Iacobucci G. Lack of investment is putting new care models at risk, think tank warns. BMJ 2016;355:i5806.
[12] Lamain-de Ruiter M, Kwee A, Naaktgeboren CA, de Groot I, Evers IM, Groenendaal F, et al. External validation of prognostic models to predict risk of gestational diabetes mellitus in one Dutch cohort: prospective multicentre cohort study. BMJ 2016;354:i4338.
[13] Damen JA, Hooft L, Schuit E, Debray TP, Collins GS, Tzoulaki I, et al. Prediction models for cardiovascular disease risk in the general population: systematic review. BMJ 2016;353:i2416.
[14] D'Amico G, Malizia G, D'Amico M. Prognosis research and risk of bias. Intern Emerg Med 2016;11:251–60.
[15] Dorresteijn JA, Kaasenbrood L, Cook NR, van Kruijsdijk RC, van der Graaf Y, Visseren FL, et al. How to translate clinical trial results into gain in healthy life expectancy for individual patients. BMJ 2016;352:i1548.
[16] Saidi O, Cordon-Cardo C, Costa J. Technology insight: will systems pathology replace the pathologist? Nat Clin Pract Urol 2007;4:39–45.
[17] Schnitt SJ. Will molecular classification replace traditional breast pathology? Int J Surg Pathol 2010; 18, 162S–166S.
[18] Vaxillaire M, Froguel P, Bonnefond A. How recent advances in genomics improve precision diagnosis and personalized care of maturity-onset diabetes of the young. Curr Diab Rep 2019;19:79.
[19] Loi S. The ESMO clinical practise guidelines for early breast cancer: diagnosis, treatment and follow-up: on the winding road to personalized medicine. Ann Oncol

2019;30(8):1183–4.
[20] Zaman A, Bivona TG. Emerging application of genomics-guided therapeutics in personalized lung cancer treatment. Ann Transl Med 2018;6:160.
[21] Dorresteijn JA, Visseren FL, Ridker PM, Wassink AM, Paynter NP, Steyerberg EW, et al. Estimating treatment effects for individual patients based on the results of randomised clinical trials. BMJ 2011;343:d5888.
[22] Debray TPA, de Jong VMT, Moons KGM, Riley RD. Evidence synthesis in prognosis research. Diagn Progn Res 2019;3:13.
[23] He C, Wang B, Wan C, Yang T, Shen Y. Diagnostic value of D2-40 immunostaining for malignant mesothelioma: a meta-analysis. Oncotarget 2017;8:64407–16.
[24] Kurzrock R, Gurski LA, Carlson RW, Ettinger DS, Horwitz SM, Kumar SK, et al. Level of evidence used in recommendations by the National Comprehensive Cancer Network (NCCN) guidelines beyond Food and Drug Administration approvals. Ann Oncol 2019. epub ahead of publication.
[25] Marchevsky AM, Walts AE, Wick MR. Evidence-based pathology in its second decade: toward probabilistic cognitive computing. Hum Pathol 2017;61:1–8.
[26] Marchevsky AM, Wick MR. Evidence-based medicine, medical decision analysis, and pathology. Hum Pathol 2004;35:1179–88.
[27] Wick MR, Marchevsky AM. Evidence-based principles in pathology: existing problem areas and the development of “quality” practice patterns. Arch Pathol Lab Med 2011;135:1398–404.
[28] Howick J. Study designs. 2019.
[29] Burns PB, Rohrich RJ, Chung KC. The levels of evidence and their role in evidence-based medicine. Plast Reconstr Surg 2011;128:305–10.
[30] Marchevsky AM, Wick MR. Evidence levels for publications in pathology and laboratory medicine. Am J Clin Pathol 2010;133:366–7.
[31] Marchevsky AM, Wick MR. Evidence-based pathology: systematic literature reviews as the basis for guidelines and best practices. Arch Pathol Lab Med 2015;139:394–9.
[32] Walts AE, Marchevsky AM. Current evidence does not warrant frozen section evaluation for the presence of tumor spread through alveolar spaces. Arch Pathol Lab Med 2018;142:59–63.
[33] Altinay S, Metovic J, Massa F, Gatti G, Cassoni P, Scagliotti GV, et al. Spread through air spaces (STAS) is a predictor of poor outcome in atypical carcinoids of the lung. Virchows Arch 2019;475:325–34.
[34] Blaauwgeers H, Russell PA, Jones KD, Radonic T, Thunnissen E. Pulmonary loose tumor tissue fragments and spread through air spaces (STAS): invasive pattern or artifact? A critical review. Lung Cancer 2018;123:107–11.
[35] Warth A. Spread through air spaces (STAS): a comprehensive update. Transl Lung Cancer Res 2017;6:501–7.
[36] Lin P, Guo YN, Shi L, Li XJ, Yang H, He Y, et al. Development of a prognostic index based on an immunogenomic landscape analysis of papillary thyroid cancer. Aging (Albany NY) 2019;11:480–500.
[37] Whittle R, Royle KL, Jordan KP, Riley RD, Mallen CD, Peat G. Prognosis research ideally should measure time-varying predictors at their intended moment of use. Diagn Progn Res 2017;1(1).
[38] Monroig-Bosque PDC, Morales-Rosado JA, Roden AC, Churg A, Barrios R, Cagle P, et al. Micropapillary adenocarcinoma of lung: morphological criteria and diagnostic reproducibility among pulmonary pathologists. Ann Diagn Pathol 2019;41:43–50.
[39] Ma M, She Y, Ren Y, Dai C, Zhang L, Xie H, et al. Micropapillary or solid pattern predicts recurrence free survival benefit from adjuvant chemotherapy in patients with stage IB lung adenocarcinoma. J Thorac Dis 2018;10:5384–93.
[40] Cao Y, Zhu LZ, Jiang MJ, Yuan Y. Clinical impacts of a micropapillary pattern in lung adenocarcinoma: a review. Onco Targets Ther 2016;9:149–58.
[41] Vollmer RT. Multivariate statistical analysis for anatomic pathology. Part II: failure time analysis. Am J Clin Pathol 1996;106:522–34.
[42] Vollmer RT. Multivariate statistical analysis for pathologist. Part I, The logistic model. Am J Clin Pathol 1996;105:115–26.
[43] Vollmer RT. Likelihood ratio vs a multivariate model. Arch Pathol Lab Med 1987;111:110–1.
[44] Moons KG, Royston P, Vergouwe Y, Grobbee DE, Altman DG. Prognosis and prognostic research: what, why, and how? BMJ 2009;338:b375.
[45] Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD). Ann Intern Med 2015;162:735–6.
[46] Burke HB. Transparent reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD). Ann Intern Med 2015;162:735.
[47] Schramm SJ, Mann GJ. Melanoma prognosis: a REMARK-based systematic review and bioinformatic analysis of immunohistochemical and gene microarray studies. Mol Cancer Ther 2011;10:1520–8.
[48] Knottnerus JA, Tugwell P. Getting more grip on genetic risk prediction studies: the GRIPS statement. J Clin Epidemiol 2011;64:817–8.
[49] Silver SA, Shah PM, Chertow GM, Harel S, Wald R, Harel Z. Risk prediction models for contrast induced nephropathy: systematic review. BMJ 2015;351:h4395.
[50] Gambino R. The misuse of predictive value—or why you must consider the odds. Ann Ist Super Sanita 1991;27:395–9.
[51] Blumberg JM. The unfolding of the CAP inspection and accreditation program. Pathologist 1979;33:406–10.
[52] Nakhleh RE. Disclosure of errors in pathology and laboratory medicine. Am J Clin Pathol 2011;135:666–7.
[53] Ahmad Z, Idrees R, Uddin N, Ahmed A, Fatima S. Errors in surgical pathology reports: a study from a major center in Pakistan. Asian Pac J Cancer Prev 2016;17:1869–74.
[54] Marchevsky AM, Gupta R. Interobserver diagnostic variability at “moderate” agreement levels could significantly change the prognostic estimates of clinicopathologic studies: evaluation of the problem using evidence from patients with diffuse lung disease. Ann Diagn Pathol 2010;14:88–93.
[55] Nicholson AG, Torkko K, Viola P, Duhig E, Geisinger K, Borczuk AC, et al. Interobserver variation among pathologists and refinement of criteria in distinguishing separate primary tumors from intrapulmonary metastases in lung. J Thorac Oncol 2018;13:205–17.
[56] Cell M Cytogenetics Committees College Of American P. Clinical laboratory assays for HER-2/neu amplification and overexpression: quality assurance, standardization, and proficiency testing. Arch Pathol Lab Med 2002;126:803–8.
[57] Moriarty AT, Bentz JS, Winkler B, Fischer AH, Laucirica R, Souers RJ, et al. The College of American Pathologists' first 3 years' experience with high-risk human papillomavirus proficiency testing for cytology and other laboratories. Arch Pathol Lab Med 2013;137:606–9.
[58] Singh V, Zwick DL, Parham DM, Heller DS. Cytology testing and proficiency: survey findings of the Practice Committee of Society for Pediatric Pathology. Pediatr Dev Pathol 2011;14:153–4.
[59] Bentz JS, Hughes JH, Fatheree LA, Schwartz MR, Souers RJ, Wilbur DC. Cytopathology Resource Committee CoAP. Summary of the 2006 College of American Pathologists Gynecologic Cytology Proficiency Testing Program. Arch Pathol Lab Med 2008;132:788–94.
[60] Ordonez NG. D2-40 and podoplanin are highly specific and sensitive immunohistochemical markers of epithelioid malignant mesothelioma. Hum Pathol 2005;36:372–80.
[61] Marchevsky AM, Wick MR. Evidence-based guidelines for the utilization of immunostains in diagnostic pathology: pulmonary adenocarcinoma versus mesothelioma. Appl Immunohistochem Mol Morphol 2007;15:140–4.
[62] Hooper JE, Geller SA. Relevance of the autopsy as a medical tool: a large database of physician attitudes. Arch Pathol Lab Med 2007;131:268–74.