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# In Reply.

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# Exploring the College of American Pathologists Electronic Cancer Checklists: What They Are and What They Can Do for You

*To the Editor*.—We read with interest the latest publication from the College of American Pathologists (CAP) on their Electronic Cancer Checklists (eCC) "Exploring the College of American Pathologists Electronic Cancer Checklists: What they are and what they can do for you."[1] This follows previous similar publications from the CAP.[2] Because there are alternatives to the eCC,[3,4] what exactly can the eCC do for me?

This article summarizes multiple features that are of benefit to pathologists creating synoptic reports, which vendors may or may not choose to implement as part of their version of the eCC. Vendors are not required to implement any of these features, the incentives for them to implement these features are not clear, and not all vendors choose to implement them. Some features may require considerable additional investment. Some features the authors describe are not currently offered as part of the eCC. As a result, this appears to be a list of what the CAP hopes the eCC will someday become rather than what is available today.

Fortunately, there are other ways to implement a synoptic report product than the one currently used for the eCC. The use of a Web site to create synoptic reports has been widely tested and validated in the literature,[3,4] and virtually all of the "advanced" features the current article describes have already been field validated and routinely used in practice since 2017. From this experience, we have learned several things that are not highlighted in this review. First, although we initially implemented "input validation" for numeric values, we subsequently removed it because the pathologists did not want to be limited to numeric values for their responses. Indeed, subsequent experience has shown that the nonnumeric portion of this response can be of substantial benefit in improving the accuracy of the reported result.[5,6] In addition, long-term collection of amendment data did not show any significant increase in amendments after this input validation was removed (Renshaw, unpublished data, June 2020). This suggests that the actual benefit of input validation of numeric values may be limited, especially if pathologists think they can improve the accuracy of their responses using an input that does not fit the validation scheme. In addition, it shows the need for actual field validation rather than simple technical software validation to determine the benefits of proposed "improvements."

Second, there is a long list of other features that can benefit pathologists including, but not limited to, custom questions, immunohistochemical support,[3] and ancillary testing, just to name a few. Why these are not discussed in the article is not clear. As an example, there was a considerable delay between the publication of the most recent International Federation of Gynecology and Obstetrics (FIGO) cervical cancer staging criteria and its subsequent incorporation into the CAP cancer checklists. To bridge this gap, we implemented a custom question to allow our clinicians to use the most up-to-date FIGO staging system without having to wait for the CAP.

We believe the successful implementation of a synoptic report product requires substantial data collection including not only software validation but also field validation to ensure that improvements to the product actually work as intended. To achieve the vision that the CAP has provided for synoptic reporting and the eCC, more active engagement by the CAP with the eCC vendors is needed to ensure the collection of those data.

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*In Reply*.—We thank the authors of the letter to the editor on our recent editorial publication "Exploring the College of American Pathologists Electronic Cancer Checklists"[1] for their interest in our work and their helpful comments, along with continuing to promote the discussion about synoptic reporting. As the College of American Pathologists (CAP) Pathology Electronic Reporting (PERT) Committee, we are committed to maintaining and helping guide development of the CAP electronic cancer checklists (eCC). We have made it a priority to publicize our processes to increase transparency to our members and colleagues about eCC development, and to welcome those who wish to make contributions. Building on this introductory editorial, we plan to publish a series of articles that will include more detailed exploration of our experience with protocol development, including supporting software tools that we have developed, approaches to past and future standardization challenges, and engagement of important stakeholders including the vendor community.

The authors of the accompanying letter present an opening question: "…what exactly can the eCC do for me?" We prefer to expand the scope to include cancer patients and the cancer control community. The use of nationally standardized and centrally managed data elements facilitate not only patient care but also interdisciplinary work across the larger stakeholder community. Indeed, in that broader context our stakeholders include our pathology community, the American Joint Committee on Cancer, the Centers for Disease Control and Prevention, the National Cancer Insti-

tute, the World Health Organization, the American Society of Clinical Oncology, the North American Association of Central Cancer Registries, the American College of Surgeons, and our laboratory information system (LIS) vendors. Since this introductory article was published, we published additional articles focused on the value of the eCC.[2,3] These publications addressed interoperability, particularly in the context of downstream, secondary use of the discretized, standardized data in the eCC. These papers were specifically targeted to our clinical colleagues to promote understanding not only of the protocols and standardized structured reporting in general, but also their roles in data exchange, the improvement of patient care, and future directions with respect to downstream use of the data. The eCC data model will become increasingly important as the 21st Century Cures Act[4] and many related rules anticipated from the Center for Medicare and Medicaid Services are implemented. The use of eCC data will allow the CAP to support pathologists with standardized, centralized solutions and to provide implementation assistance to meet these governmental mandates while lowering the burden on pathologists. We hope that these publications, along with our future publications, will promote better understanding of the value of the CAP Cancer Protocols and corresponding eCC, as well as reinforce the central role of our pathology specialty within the future of healthcare informatics.

The authors point out some of the complexities innate to our relationships with the anatomic pathology LIS vendors that implement the electronic cancer protocols. Indeed, vendors are not required to implement any of the ergonomic features outlined in our article, in particular those that may require additional investment. However, vendors are also sensitive to customer needs and demands as systems evolve. Furthermore, the purpose of discussing expected vendor functionality in our article was particularly to encourage the pathology user community to directly question their vendor as to why they cannot perform specific functions described by the CAP. A full discussion of the challenges inherent to the vendor implementation process was outside the scope of our introductory article. Subsequent publications will expand upon successes and challenges in this realm. These will include descriptions of our direct LIS vendor engagement project via the Vendor Implementation Collaboration program, which has already yielded excellent progress toward building symbiotic relationships between CAP and the LIS vendors grounded in knowledge sharing, a deeper understanding of implementation methods, the relevant barriers to full implementation, and ways in which we can work together to improve the final products used in pathologists' daily workflow. The vendors are also surveyed regularly with respect to the functionality currently available on a vendor basis. Individual vendors can see their responses (deidentified) compared with their "peers." This has been well received in the industry and we have already started to see major advancements in eCC functionality being offered.

Another item specifically mentioned in the letter to the editor was the utilization of nonnumeric operators in the acquisition of numeric data, such as "at least" or "greater than" in the context of an argument against requiring input validation of numeric values. Indeed, we do include a choice to use a number of these operators in the context of collecting a numeric value, which we validate as a numeric response to facilitate its downstream reuse as a number value. Without this specification, some of the analytics applied to the numerical data would fail. With the understanding that an exact number or even a minimum or maximum value might not be attainable, we routinely include an option to indicate that such a value cannot be reported with a free-text field to explain. Our goal is to encourage the community to use interoperable values as much as possible, but we do understand the need for flexibility for special cases.

The letter to the editor also mentioned the development and maintenance of web-based synoptic reporting or traditional "canned text" synoptic free-text forms as alternative reporting options that are certainly valid. In fact, there are several "alternatives" to the CAP eCC and the purpose of the article was not intended to be promotional. Rather, it was meant to clearly state the benefits of discretized data and the need for our peers to help push their vendors to provide the best solutions possible. We note that members of the involved CAP committees have previously implemented their own web-based solution[5] and subsequently used vendor-implemented eCC. They have commented that the in-house web-based solution is more difficult to maintain and update as new protocol versions are released. In addition, important considerations for adopting such tools are interoperability across electronic health care systems and exchange and reuse of the data by stakeholders, such as disease registries, along with data access control and adherence to federal regulations concerning protected health information. We outline and illustrate in our publications the importance of downstream interoperabilty and electronic reuse of the data that is best achieved via integrated electronic synoptic reporting systems based in a common standardized language and format.

The authors also mention several other features that could benefit pathologists that were not addressed in our publication. We agree with the authors on the value of implementing immunohistochemical support and ancillary testing to the diagnostic output rendered by an electronic diagnostic cancer checklist. Although not explicitly mentioned in our introductory publication, biomarker templates are available and integral parts of the CAP Cancer Protocols and available to be implemented in the LIS workflow, although not required for accreditation. It is the purpose of these templates to use structured data capture to limit the use of custom questions in favor of validated data standards using metadata that can be stored in a data repository to facilitate data interoperability and reuse.

Last, software and field validation is an integral part of the CAP PERT Committee workflow before the publication of electronic cancer checklists. This validation process will be more specifically addressed in a future publication focused on the informatics infrastructure that supports the development of the CAP eCC.

The development of data element content (Word and PDF versions) and electronic implementation of the eCC is overseen by 2 CAP committees (Cancer Committee and PERT) and CAP staff. Feedback from our users is integral to accomplishing these goals and creating the best product available to help direct patient care. We thank the authors for their letter to the editor. Comments or questions on

the protocols in electronic or paper version can be emailed to the committee at cprotoc@cap.org.

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## Antibodies to Extractable Nuclear Antigens Are Detectable in a Considerable Number of Sera That Test Negative for Antinuclear Antibodies

*To the Editor*.—The number of patients with negative antinuclear antibodies (ANAs) and positive extractable nuclear antigen antibodies (ENAs) appears to be greater than we expected. However, medical colleges[1] and insurance companies support the performance of ENA testing only in patients with positive ANAs, or in a few cases with suspicions of Sjögren syndrome, suspicions of myositis, or suspicions of systemic lupus erythematosus (SLE) with ANA negativity, and algorithms that consider this criterion have been designed to optimize ENA indications.[2] This study was proposed to evaluate the frequency of cases with negative ANAs and positive ENAs in a cohort of 2510 patients with suspected systemic autoimmune disease of the connective tissue.

Tests were run between January 1999 and December 2014 in a private clinical laboratory by the same technician. The requests were made by any doctor who suspected a systemic autoimmune disease. By indirect immunofluorescence microscopy, ANA and anti-centromere antibodies were made using Hep2 cells (DiaSorin, Saluggia, Italy) as a substrate starting from a 1:80 dilution. Hep2 ANA tests were performed and interpreted following the American College of Rheumatology (ACR) recommendations.

Using enzyme-linked immunosorbent assay, antibodies were determined against the following extractable nuclear antigens (1:100 dilution): Sm, RNP, Jo-1, Scl-70, SSA (Ro), and SSB (La) (DiaSorin).

Among the 2510 ENA studies performed in combination with ANAs, 2128 (84.8%) were performed in women and 382 (15.2%) in men. We found that 86 of the 2510 cases (3.4%) were negative to ANAs but positive against at least 1 antigenic subspecificity of ENA, distributed as follows: 47 with only anti-SSA, 8 only with anti-SSB, 5 with anti-SSA and anti-SSB, 1 with anti-SSB and anti-RNP, 7 with only anti-RNP, 1 with only anti-RNP, 3 with anti–Scl-70, 2 with anti–Scl-70 and anti-SSA, 1 with anti–Scl-70 and anti-SSB, 5 with anti–Jo-1, and 4 with anti-centromere.

The association of ANAs and ENAs with each other and with the sexes is shown in the Table. As we expected, the strength of the association was more relevant in men with ANA-negative, ENA-negative antibodies and in women with ANA-positive, ENA-positive antibodies ($\chi^2 = 33.689$; degrees of freedom = 3; $P < .001$).

The ANA-negative, anti-ENA–positive group represented 3.4% of all patients (86 of 2510), and 91.86% (79 of 86) of this subgroup was represented by women. The number of patients does not seem to correspond in all cases to some positive forms of anti–Jo-1 myositis and negative ANA, or to cases with SLE or Sjögren syndrome with positive SSA and negative ANA[3] because the frequency of these conditions is low. For example, it has been estimated that approximately 3% of