



COLLEGE of AMERICAN  
PATHOLOGISTS

# ARCHIVES

of Pathology & Laboratory Medicine

## **EARLY ONLINE RELEASE**

Note: This article was posted on the *Archives* Web site as an Early Online Release. Early Online Release articles have been peer reviewed, copyedited, and reviewed by the authors. Additional changes or corrections may appear in these articles when they appear in a future print issue of the *Archives*. Early Online Release articles are citable by using the Digital Object Identifier (DOI), a unique number given to every article. The DOI will typically appear at the end of the abstract.

The DOI for this manuscript is doi: [10.5858/arpa.2019-0474-OA](https://doi.org/10.5858/arpa.2019-0474-OA)

The final published version of this manuscript will replace the Early Online Release version at the above DOI once it is available.

# Pathology Laboratory Policies and Procedures for Releasing Diagnostic Tissue for Cancer Research

Yao Yuan, PhD, MPH; Alison L. Van Dyke, MD, PhD; Valentina I. Petkov, MD, MPH; Sarah Hussey, MS; Radim Moravec, PhD; Sean F. Altekruise, DVM, PhD, MPH; Mayra Sandoval; Rosemary D. Cress, DrPH, MPH; Lloyd M. Mueller, PhD; Alan Mogi; Brenda Y. Hernandez, PhD, MPH; Freda R. Selk, RHIT; Charles F. Lynch, MD, PhD; Thomas C. Tucker, PhD, MPH; Mary Anne Lynch, MPH; Christina Lefante, MPH; Xiao-Cheng Wu, MD, MPH; Carol Sweeney, PhD; Jennifer A. Doherty, PhD, MS; Lynne S. Penberthy, MD, MPH

• **Context.**—The Surveillance, Epidemiology, and End Results (SEER) cancer registry program is currently evaluating the use of archival, diagnostic, formalin-fixed, paraffin-embedded (FFPE) tissue obtained through SEER cancer registries, functioning as honest brokers for deidentified tissue and associated data. To determine the feasibility of this potential program, laboratory policies for sharing tissue for research needed to be assessed.

**Objective.**—To understand the willingness of pathology laboratories to share archival diagnostic tissue for cancer research and related policies.

**Design.**—Seven SEER registries administered a 27-item questionnaire to pathology laboratories within their respective registry catchment areas. Only laboratories that

processed diagnostic FFPE specimens and completed the questionnaire were included in the analysis.

**Results.**—Of the 153 responding laboratories, 127 (83%) responded that they process FFPE specimens. Most (n = 88; 69%) were willing to share tissue specimens for research, which was not associated with the number of blocks processed per year by the laboratories. Most laboratories retained the specimens for at least 10 years. Institutional regulatory policies on sharing deidentified tissue varied considerably, ranging from requiring a full Institutional Review Board review to considering such use exempt from Institutional Review Board review, and 43% (55 of 127) of the laboratories did not know their terms for sharing tissue for research.

**Conclusions.**—This project indicated a general willingness of pathology laboratories to participate in research by sharing FFPE tissue. Given the variability of research policies across laboratories, it is critical for each SEER registry to work with laboratories in their catchment area to understand such policies and state legislation regulating tissue retention and guardianship.

(*Arch Pathol Lab Med.* doi: 10.5858/arpa.2019-0474-OA)

With the rise of personalized medicine for cancer treatment, there is an increasing demand to profile molecular features of tumors.<sup>1</sup> Not only is the procedure for acquiring fresh tumor specimens costly and not always feasible, but researchers collecting such tissue specimens do not always have access to clinical records and long-term follow-up information. Additionally, such investigator-initiated and pharmaceutical company-sponsored studies are not necessarily representative of the US population.<sup>2-4</sup> One alternative source of tissue from cancer patients is archival formalin-fixed, paraffin-embedded (FFPE) tissue, routinely collected in clinical practice for diagnostic purposes.

The Surveillance, Epidemiology and End Results (SEER) cancer registry system, sponsored by the National Cancer Institute (NCI), is a unique data resource that routinely collects data on all incident cancer cases, including long-term follow-up information. The NCI's Surveillance Research Program, which oversees the SEER registries, is currently investigating the feasibility of a Virtual Tissue Repository (VTR) to establish an infrastructure for acquisition of

Accepted for publication March 31, 2020.

Supplemental digital content is available for this article. See text for hyperlink.

From the Surveillance Research Program, Division of Cancer Control and Population Sciences (Drs Yuan, Van Dyke, Petkov, Hussey, and Penberthy), and the Cancer Diagnosis Program, Division of Cancer Treatment and Diagnosis (Dr Moravec), National Cancer Institute, National Institutes of Health, Rockville, Maryland; the HIV/AIDS Program, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland (Dr Altekruise); the Cancer Registry of Greater California, Department of Public Health, Sacramento (Ms Sandoval and Dr Cress); the Connecticut Tumor Registry, State Department of Public Health, Hartford (Dr Mueller); the Hawaii Tumor Registry, University of Hawaii Cancer Center, Honolulu (Mr Mogi and Dr Hernandez); the Iowa Cancer Registry, The University of Iowa, Iowa City (Ms Selk and Dr Lynch); the Kentucky Cancer Registry, University of Kentucky, Markey Cancer Center, Lexington (Dr Tucker); the Louisiana Tumor Registry, Louisiana State University School of Public Health, New Orleans (Mss Lynch and Lefante and Dr Wu); and the Utah Cancer Registry (Drs Sweeney and Doherty) and Huntsman Cancer Institute (Dr Doherty), University of Utah, Salt Lake City.

This study was funded by the National Institutes of Health through contracts HHSN261201300009I, HHSN261201300013I, HHSN261201300014I, HHSN261201300016I, HHSN261201300019I, HHSN261201300020I issued to the 6 SEER cancer registries. The authors have no relevant financial interest in the products or companies described in this article.

Corresponding author: Yao Yuan, PhD, MPH, Division of Cancer Control and Population Sciences, National Cancer Institute, National Institutes of Health, 9609 Medical Center Dr, Rockville, MD 20850 (email: yao.yuan@nih.gov).

deidentified clinical data, tissue resources, and whole slide images for cancer research at the population level. Researchers will be able to apply to access a searchable, web-based interface to select cancer cases ascertained within geographic areas covered by participating registries. The SEER registries will function as honest brokers to supply deidentified but linked tissue and data. It is anticipated that 2 funding sources will be available for the future scaled VTR. The NCI will provide funding for personnel and technologic infrastructure, and researchers using this resource will pay a fee for services rendered by and through the registries. Pathology departments and/or laboratories providing requested services (eg, sharing tissue, whole slide imaging, pathologist review, etc) will be able to recoup costs incurred directly through the SEER registries. Importantly, for tissue-based research projects using the future VTR, researchers will be required to deposit results from SEER-linked VTR studies in a data sharing platform. It is envisioned that the NCI will need to work with organizations like the College of American Pathologists (CAP), the United States and Canadian Academy of Pathology, the American Society of Clinical Oncology, the American Association for Cancer Research, patient advocates, and other stakeholders to communicate the value of VTR as a resource for cancer research.

We are conducting a VTR pilot program, which is providing a wealth of information to inform feasibility and best practices for our proposed VTR program. As part of this pilot, a laboratory evaluation was conducted to understand the policies and practices of pathology laboratories concerning sharing archival diagnostic and resection FFPE tissue specimens for research and to assess the feasibility of conducting research using these tissue resources from pathology laboratories within catchment areas of participating SEER registries.

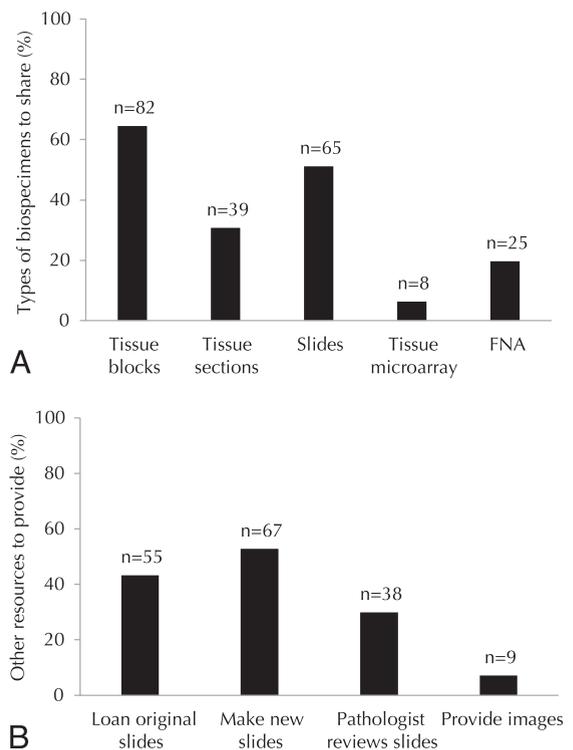
## MATERIALS AND METHODS

Between April 2016 and February 2017, seven SEER registries (Greater California, Connecticut, Hawaii, Iowa, Kentucky, Louisiana, and Utah) participated in a pathology laboratory evaluation. A 27-item questionnaire was administered via telephone by the registry to a representative from each pathology laboratory, either freestanding or in a hospital, that handles general cancer specimens within the registry's catchment area. Deidentified responses were submitted by registries to the NCI's Surveillance Research Program through Lime Survey.<sup>5</sup> Laboratories reporting that they do not process FFPE tissue blocks were excluded from answering further related questions. Pathology laboratory evaluation questions were formulated to address 4 major areas: biospecimen storage, research collaboration, digital slide imaging, and research approval (Supplemental Table 1, see [supplemental digital content](#), containing 1 figure and 10 tables).

Frequency distributions of laboratory responses were calculated. The number of FFPE tissue blocks processed per year by laboratories was used as a proxy measurement for laboratory size (>0 to <10 000, 10 000 to <100 000, and ≥100 000). The association between number of FFPE tissue blocks processed per year and willingness to share tissue for research was evaluated using Fisher exact test. Statistical analysis was conducted using StataSE 15 (StataCorp LLC, College Station, Texas) and SAS 9.4 (SAS Institute Inc, Cary, North Carolina), with the threshold for significance established at  $P < .05$ .

## RESULTS

Numbers of laboratories within each SEER registry's catchment area that responded to the evaluation varied considerably. Of the 250 laboratories within the 7 SEER registries' catchment areas, 153 (61%) responded to and



**Figure 1.** Pathology laboratories' current practice on sharing of biospecimens or providing other resources or services for research use ( $n = 127$ ). The willingness to share different types of biospecimens for research use (A), and the willingness of providing other resources or services for research (B). Abbreviation: FNA, fine-needle aspiration.

completed the evaluation. Response proportions varied by registry, ranging from 48% to 83% (Supplemental Table 2). Among the laboratories that completed the evaluation, 127 (83%) reported that they process FFPE blocks and therefore were asked to complete the full questionnaire.

Most of the laboratories queried (88 of 127; 69%) indicated that they were willing to share tissue specimens for research purposes (Supplemental Table 2). Most of the laboratories processed between 10 000 and 100 000 tissue blocks per year, and the laboratory size was not associated with willingness to share tissue blocks or sections for research (Supplemental Table 3). Among the laboratories that were not willing to share diagnostic tissue for research, underlying reasons included administrative costs, concern about depleting resources, unwillingness to participate in research, and the need to retain blocks for legal issues or future diagnostic studies (Supplemental Table 4). Most of the laboratories were willing to share tissue blocks for research (82 of 127; 65%) and provide other services (eg, loan slides or provide digital slide images) to researchers (Figure 1).

Costs associated with retrieving, processing, and/or shipping tissue for research varied across different laboratories for the same type of requests (summarized in Supplementary Tables 5, through 9, and original answers listed in Supplementary Table 10). For example, 55 of 127 laboratories (43%) were willing to loan original diagnostic slides (Figure 1), 25 of which (45%) loaned slides at no extra charge (shipping cost may apply), and a few laboratories estimated the cost being between \$5 and \$26 per slide (Supplementary Table 5). A total of 67 of the 127

Storage of Formalin-Fixed, Paraffin-Embedded (FFPE) Specimens at Different Locations		
Length of Storage, y	Location of Tumor FFPE Block Storage, No. (%) <sup>a</sup>	
	In Laboratory	Remote Site
0	1 (1)	62 (49)
>0 to <5	36 (28)	0 (0)
5 to <10	7 (5)	10 (8)
10 to <15	64 (50)	23 (18)
15 to <100	7 (5)	12 (9)
Indefinitely	7 (5)	12 (9)
Unknown	5 (4)	8 (6)
<b>Total</b>	<b>127</b>	<b>127</b>

<sup>a</sup> Percent of the total.

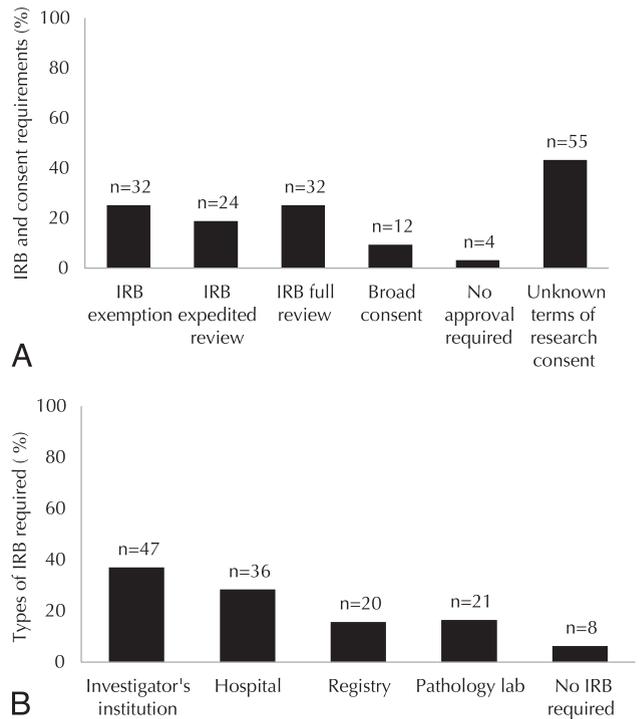
laboratories (53%) were willing to generate new slides from FFPE tissue blocks (Figure 1), and 43 of them (64%) provided an estimated fee (Supplementary Table 6), ranging from no charge (5 of 67; 7.5%) to \$200 per slide (1; 2%), with most (40 of 67; 60%) charging less than \$25 per slide. Fewer laboratories reported that they provide slide review by a pathologist for tissue block selection (38 of 127; 30%) or of digital slide images (6 of 127; 5%; Figure 1 and Supplementary Tables 7 and 8, respectively). Among laboratories willing to share tissue for research (n = 88), most of them (53; 60%) did not know or did not provide the cost estimates to retrieve tissue blocks. For the 40% (35 of 88) that provided cost estimates, 19 of 88 (22%) charge \$30 or less for tissue block retrieval, and 13 of 88 (15%) do not charge (Supplementary Table 9).

Of the laboratories that processed tumor FFPE blocks (n = 127; Table 1), approximately half responded that they do not store tissue blocks at a remote site. Although 60% of the 127 laboratories reported that they kept tissue blocks for 10 to 15 years either onsite or at offsite storage sites (Table 1), another 13% stored FFPE tissue blocks indefinitely. Almost 75% (93 of 127) of responding laboratories discarded FFPE blocks before or upon reaching the 10-year tissue block storage time as required by CAP (Supplemental Figure 1, A). The most frequent reason for destroying FFPE blocks was meeting the CAP minimum requirement for retaining diagnostic FFPE tissue blocks (76 of 93; 82%; Supplemental Figure 1, B). Another frequent reason for discarding tissue was the cost and space associated with storage (33 of 93; 35%; Supplemental Figure 1, B).

The human subjects research requirements for conducting research using human biospecimens also differed by laboratory (Figure 2). Varying levels of Institutional Review Board (IRB) approval were required for laboratories to provide biospecimens for research purposes (eg, IRB exemption of review, expedited, or full IRB review required). Regarding informed consent, 55 of 127 laboratory respondents (43%) reported that they did not know the current requirements of consent for research purposes (Figure 2, A). The most commonly reported IRB approval requirements were IRB approval from a principal investigator's institution (47 of 127; 37%) or from a hospital (36 of 127; 28%; Figure 2, B).

## DISCUSSION

Registry-based biospecimen repositories have provided invaluable opportunities in cancer research,<sup>6</sup> especially with recent developments in cancer genomics research.<sup>7,8</sup> We



**Figure 2.** Regulatory requirements for research using biospecimens among laboratories processing formalin-fixed, paraffin-embedded blocks (n = 127). A, Terms of research consent required for pathology laboratories to provide tissue specimens for research. B, Institutional Review Board (IRB) protocols required by pathology laboratories.

sought to understand the policies and procedures for obtaining archival diagnostic FFPE specimens for use in cancer research through SEER cancer registries. The study not only provided an encouraging perspective on the potential availability and storage capacity of archival tissue blocks but also raised the concern of the policies affecting laboratories' willingness to share such tissue for correlative research unrelated to a patient's clinical care. These findings will help address the gaps and strengthen the collaborations between the research community and surgical pathology laboratories.

Our study achieved an overall response rate of 61%, underlying the importance of a familiar working relationship between cancer registry staff and personnel at laboratories for the high participation in the pathology laboratory evaluation. However, given the variability in response rates of laboratories among these registries, it is plausible that how the registry staff approached laboratory staff and directors impacted their willingness to complete the assessment. These considerations may not fully explain the lower than desired response rate, because vigilant follow-up was reported from registries, but responses from some laboratories were incomplete.

Because most laboratories responding to the survey were willing to share tissue blocks and to offer additional tissue resources and services for correlative research, use of such resources for population-based research appears feasible, regardless of laboratories' capacity to process FFPE tissue. Only a few laboratories clearly stated their reasons for not sharing tissue for research, which included scientific, administrative, and legal reasons. Fees associated with retrieving tissue for research could be a major concern for

researchers, and they may also impact cost recovery for the service provided by the laboratories. Among laboratories providing tissue-related services for certain fees, it is important to have cost-recovery mechanisms in place so that laboratories will be able to continue supporting tissue- and digital image-based research. It is anticipated that laboratories with a “research support cost-recovery core” may have their own digital slide imaging platform that would allow them to provide 40× magnification whole slide imaging files to SEER without incurring shipment-related risks of damaging or losing original glass slides. Although the ownership of diagnostic tissue blocks is not stated in state or federal rules, it is recognized that pathology laboratories are the custodians of such diagnostic tissue.<sup>9</sup> Although using such diagnostic FFPE tissue for correlative research is not prohibited by law, pathology laboratories prioritize use of clinical specimens for diagnosis and patient management, resulting in limitations on the availability and quantity of such tissue that can be shared with researchers.<sup>10</sup>

Almost all laboratories reported that they stored FFPE tissue blocks on-site for up to a certain period of time, generally around 10 years. Most laboratories that were willing to share tissue for research had FFPE blocks readily available for retrieval. However, given the CAP requirement of retaining FFPE tissue blocks for at least 10 years,<sup>11</sup> many laboratories indicated that they would terminate block storage and destroy blocks upon meeting this 10-year retention requirement. Since 2003, three SEER registries (Hawaii, Iowa, and Los Angeles) have functioned as Residual Tissue Repositories that collect FFPE tissue blocks being discarded by laboratories after the minimum retention requirement has been met as established by CAP.<sup>12</sup> Investigators can request deidentified, but linked, tissue and data through these Residual Tissue Repositories, which acquire discarded tissue from laboratories in their catchment area on an annual basis. Simultaneously, these registries can obtain medical records to provide additional clinical information and deidentified pathology reports. As the future SEER-linked VTR Program is developed, it will be critical to concurrently expand the Residual Tissue Repositories system. Although concerns were raised regarding the usability of older FFPE tissue for DNA and RNA studies,<sup>13,14</sup> there have been successes in using such decades-old FFPE specimens acquired from the SEER-linked Residual Tissue Repositories for next-generation sequencing studies.<sup>7,8</sup>

As expected, laboratory willingness to provide diagnostic tissue resources or services for research requires some level of IRB review and, in some cases, informed consent.<sup>15</sup> One explanation for laboratory respondents’ indication that they did not know whether they would require IRB review and/or informed consent was that they may not have previously participated in research. At the time this pathology evaluation was conducted, there were nationwide debates about the Notice of Proposed Rulemaking to the Federal Policy for the Protection of Human Subjects published in the Federal Register on September 8, 2015.<sup>16</sup> The Notice of Proposed Rulemaking proposed that all research using deidentified human biospecimens be subject to the Common Rule and that consent be obtained for such research. This proposal could have impacted how the laboratories responded to questions regarding IRB requirements and the need for informed consent for sharing deidentified specimens. However, the Final Rule, published in the *Federal Register* on January 17, 2017, and made effective on January

21, 2019, did not adopt the proposed changes regarding the use of deidentified biospecimens.<sup>16</sup> Under the Final Rule, studies involving deidentified biospecimens and data are not considered human subjects research and therefore are not regulated by the Common Rule. Another explanation could be that for laboratories that had experiences in handling tissue requests for nondiagnostic purposes, the model of participating in research as described in the questionnaire may be unfamiliar to the respondents. For example, most laboratories were familiar with the use of diagnostic tissue for clinical trials whereby a written informed consent is obtained and residual tissue is sent to the clinical trial team.<sup>17</sup>

This study had both strengths and limitations. First, the study included both research institute-affiliated and free-standing community pathology laboratories within population-based SEER registry areas, thus providing generalizable perspectives of pathology laboratories. Also, laboratories could have updated their policies since the time the study was conducted; therefore, the results presented in this paper may not accurately reflect current practice. However, with the ongoing VTR pilot studies, new insights into current practice have been and will be provided as FFPE specimens are requested and processed.

## CONCLUSIONS

This evaluation of community-based and academic pathology laboratories demonstrates the feasibility of obtaining archival, diagnostic FFPE tissue specimens for research on a population level. Institutional regulatory policy is the primary factor restricting the pathology laboratories from participating in research, and these policies vary by institution. Increasing laboratories’ awareness of the current Final Rule for research involving deidentified biospecimens may assist with access to tissue for nonclinical purposes in the future. The development of an infrastructure for researchers to access deidentified diagnostic FFPE tissue and data will require the engagement of laboratories and affiliated pathologists, hospitals, researchers, policy makers, and patient advocacy groups.

## References

1. Collins FS, Varmus H. A new initiative on precision medicine. *N Engl J Med*. 2015;372(9):793–795.
2. Naranjo CM. Special populations underrepresented in oncology research: challenges and solutions to engage the Hispanic population. <http://www.appliedclinicaltrials.com/special-populations-underrepresented-oncology-research-challenges-and-solutions-engage-hispanic-popu>. Accessed May 2, 2019.
3. Ragin C, Park JY. Biospecimens, biobanking and global cancer research collaborations. *Ecanmedscience*. 2014;8:454.
4. Woodcock J, Whyte J, Henderson MB. Global participation in clinical trials report. <https://www.fda.gov/media/106725/download>. Accessed December 12, 2019.
5. The Lime Survey Web site. <https://www.limesurvey.org/>. Accessed May 2, 2019.
6. Altekruse SF, Rosenfeld GE, Carrick DM, et al. SEER cancer registry biospecimen research: yesterday and tomorrow. *Cancer Epidemiol Biomarkers Prev*. 2014;23(12):2681–2687.
7. Carrick DM, Mehaffey MG, Sachs MC, et al. Robustness of next generation sequencing on older formalin-fixed paraffin-embedded tissue. *PLoS One*. 2015; 10(7):e0127353.
8. Zhao Y, Mehta M, Walton A, et al. Robustness of RNA sequencing on older formalin-fixed paraffin-embedded tissue from high-grade ovarian serous adenocarcinomas. *PLoS One*. 2019;14(5):e0216050.
9. Dry S. Who owns diagnostic tissue blocks? *Lab Med*. 2009;40(2):69–73.
10. McDonald SA, Chernock RD, Leach TA, et al. Procurement of human tissues for research banking in the surgical pathology laboratory: prioritization practices at Washington University Medical Center. *Biopreserv Biobank*. 2011; 9(3):245–251.
11. College of American Pathologists (CAP) retention of laboratory records and materials. <https://www.nclleg.gov/documentsites/committees/PMC-LRC2011/>

December%205,%202012/College%20of%20American%20Pathologist%20Retention%20Policy.pdf. Accessed May 2, 2019.

12. Residual Tissue Repository (RTR) Program Web site. <https://seer.cancer.gov/biospecimen/>. Accessed January 13, 2020.

13. Watanabe M, Hashida S, Yamamoto H, et al. Estimation of age-related DNA degradation from formalin-fixed and paraffin-embedded tissue according to the extraction methods. *Exp Ther Med*. 2017;14(3):2683–2688.

14. Bonnet E, Moutet ML, Baulard C, et al. Performance comparison of three DNA extraction kits on human whole-exome data from formalin-fixed paraffin-embedded normal and tumor samples. *PLoS One*. 2018;13(4):e0195471.

15. Allen MJ, Powers ML, Gronowski KS, Gronowski AM. Human tissue ownership and use in research: what laboratorians and researchers should know. *Clin Chem*. 2010;56(11):1675–1682.

16. Federal policy for the protection of human subjects 2015. *Fed Regist*. 2015; 80(173):53933–54061. <https://www.federalregister.gov/documents/2015/09/08/2015-21756/federal-policy-for-the-protection-of-human-subjects>. Accessed December 12, 2019.

17. McCall SJ, Dry SM. Precision pathology as part of precision medicine: are we optimizing patients' interests in prioritizing use of limited tissue samples? *JCO Precis Oncol*. 2019(3):1–6.