SPECIMEN COLLECTION WITHIN THE CRN:

A CRITICAL APPRAISAL

A Report Produced by

The CRN Pharmacovigilance Project Genomics Working Group

The goal of this document is to describe what we know about existing repositories, and related resources, at participating CRN sites. Through describing these repositories and resources, we can identify future needs and goals for gathering specimens for use in future genomic research within the CRN.

The HMO CRN Cancer Research Network

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Executive Summary

Purpose

The overall goal of the genomics working group (GWG) was to explore issues surrounding the collection and use of biological specimens at the participating CRN sites. To better understand the capabilities of each site to provide existing specimens, or to collect samples de-novo, we performed the tasks and collated the data listed below:

Summary of Tasks

1. We assessed the type and number of specimens that are currently available for genomic studies. Information included how each specimen was stored.
2. We collected site-specific data about recruitment procedures and participation rates from past studies that collected specimens.
3. We assessed the feasibility of various recruitment procedures at CRN sites.
4. We developed study documents including recruitment letters and informed consent forms for collection of both saliva and blood specimens (Appendix 2 & 3).

Primary Conclusions

1. There is a limited number of sites with large scale (>20,000) collection of specimens for broad research purposes within the CRN, indicating a clear need for additional specimen collection at sites to facilitate future research.
2. It can be a challenge to identify individuals with specimens available for research.
3. Some sites do not have formal written policies and procedures for utilizing the specimens that have been collected.
4. Almost all sites have stored tumor samples for research purposes, but current storage methodology often is not adequate for some genomics research.
5. There is a trade-off in recruitment between breadth of data collection and participation rate which is not unique to genetic studies.
6. The consent process for genetic studies requires specific considerations in order to address people's fears and local variations in laws regarding genetic research and privacy.

Recommendations for Future Work

1. Funding sources should be identified to:
   a. re-consent subjects at KPNW to allow use of existing samples for other studies,
   b. increase the number and diversity of samples at all sites, and
   c. allow for pathologist time and support at sites with stored samples.
2. Indicator variables should be added to the VDW indicating the availability of various specimens at the individual sites. Additionally, on a broader scale, a database of studies should be developed to share information about what samples even exist at the sites.
3. A website with best practices regarding biological specimen collection and use should be developed and maintained by the CRN.
4. Sites should develop the storage methodology and infrastructure to allow use of stored pathology samples for genomic research purposes.

5. Studies need to spend considerable effort determining the amount of data and sample size necessary for the research question in order to achieve the best balance of sample accrual methodology, number of study activities, and participation rate.
6. Sites should utilize best practice resources in developing consent forms and recruitment processes for genetic studies.

Limitations

The information on biological specimen resources documented in this report is limited by factors related to the aims of the CRN Pharmacovigilance study. Although every effort was made by the GWG to make this report comprehensive, the scope of work was bound by these two factors.

1. The survey was limited to sites that were participating in the CRN Pharmacovigilance study, which was 8 out of the 14 CRN sites.
2. Not all repository resources are represented because of the focus on breast cancer in the CRN Pharmacovigilance study. For example, at GHC, there is a large repository of specimens from Alzheimer's Disease patients that is not reflected in this report.

Task 1: We assessed the availability of specimens for all cancer studies

Deliverable: A catalog of available bio-specimens for cancer pharmacovigilance studies

Method: To provide information to researchers about availability and accessibility of existing specimens, we developed and distributed a survey to all CRN PIs at all CRN sites participating in the pharmacovigilance pilot project (see Appendix 1).

Key Findings:

- This study exposed an important barrier to future research: lack of systematic documentation of existing or past studies at each site where specimen collection took place. Current practice is to rely on the institutional memories of current staff. **We recommend the development of a 'data base of studies' to facilitate identification of specimen collections in the future. Appendix 5 includes a list of proposed variables that would be captured in this database.**

- Only two sites (MFRC and KPNC) currently have a large-scale repository (>20,000) of banked blood or saliva specimens that were collected under protocols that allow broad access for future research. KPNC has a repository with ~100,000 saliva samples, and MFRC has a repository with ~20,000 samples including DNA, plasma, and serum. **We recommend that an indicator variable be added to the VDW at these two sites to identify patients who have a specimen available in the repository. As other sites develop similar resources, we recommend that they populate similar variables within the VDW.**

- One site (KPNW) has two large-scale studies (>20,000 subjects each) with banked specimens (blood and cervical vaginal lavage). These samples could provide DNA for future cancer research studies. However, in order to conduct additional studies of cancer on specimens from one of these studies, re-consent of subjects as well as permission from NHLBI would be required to obtain the samples. Permission from the PI and re-consent of subjects would be necessary to utilize samples from the other study, depending on the scope of the project. **We recommend identifying a funding source that will facilitate re-consent of these subjects, in order to fully make use of these specimens.**

- Aside from the studies listed above, the number of existing specimens from breast-cancer patients is limited to <4,700 subjects across all sites (Table 2).

- Multiple CRN sites (Table 1) have access to banked tumor blocks, often going back over multiple years (to 1960), through pathology departments. However, nearly all sites store samples as formalin-fixed paraffin-embedded (FFPE) tumor blocks, which have limited utility for genomics research (the exception is MFRC). None of the sites currently store fresh frozen tissue as a standard procedure. Some sites have experience utilizing their specimen banks and a well-established infrastructure that facilitates access to specimens. Such infrastructure includes written policies and procedures, data-access committees, and established pricing structures. **We**

recommend that sites without infrastructures in place, using resources at other sites as a model, should develop procedures to facilitate access to these important resources. Appendix 6 includes documentation of procedures and policies developed by existing sites.

- Whole blood or blood components are the most commonly collected specimen types. Only two studies (the KPNC repository and a study at KPG) collected saliva specimens (Table 2).
- With the exception of the large scale repositories listed above, existing specimens are insufficient; new specimen collection will be needed for a variety of future research, including breast cancer research.

Table 1. Existing Tumor Repository Resources

Site	Tumor Repository Present	Method of Storage	Written Policies and Procedures	Data Access Committee	Established Price Structure	Experience Using Resource	Contact e-mail
KPCO	✓(1990)[3]	FFPE	*	*	*	*	Heather.S.Feigelson@kp.org
KPG	*	*	*	*	*	*	Robert.L.Davis@kp.org
KPH	✓ (1983)	FFPE	✓[1]	✓[1]	✓[1]	✓	Stacey.Honda@kp.org
KPNC	✓(1970)[2]	FFPE	✓	✓	✓	✓	Judith.C.Morse@kp.org
KPSC	✓	FFPE	✓	✓	✓	✓	Reina.Haque@kp.org
KPNW	✓ (1960)	FFPE	IP	✓	IP	✓	Katrina.Goddard@kpchr.org
MCRF	✓(25 yrs)	AFF/NBF	*	*	*	✓	Mccarty.Catherine@mcrf.mfldclin.edu
HPRF	✓(20 yrs)	FFPE	✓	*	*	✓	Pamala.A.Pawloski@HealthPartners.com
GHC	✓ (1977)	FFPE	IP	IP	IP	✓	Vanneman.N@ghc.org
HFHS	✓ (1989)	FFPE	*	*	*	✓	Cdudas1@hfhs.org (Christine Neslund-Dudas)
HPHC	✓(10 yrs)	FFPE	*	*	*	✓	Larissa_Nekhlyudov@harvardpilgrim.org

FFPE: Formalin-fixed, Paraffin-embedded; AFF: acid formalin-fixed; NBF: neutral buffer fixed

✓= available; * = not available; IP: in progress

[1]Specimens more than 10 years old are held in a repository with established policies and procedures. Specimens less than 10 years old are accessible through the KPH pathology department.

[2]Blocks are retained since 1970 for most KPNC facilities, although slides may be destroyed after 10 years.

[3]Even older specimens may be available depending on the location of the specimen.

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Table 2. We assessed whether, and what, existing specimens from breast-cancer patients are currently available.

During what time frame did recruitment take place? (Q3)	Prior to 2000: Five studies. 2000-2005: Six studies. After 2005: Nine studies.
Is the study or repository still open to recruitment? (Q4)	Eight studies are still open to recruitment.
How many subjects were the studies aiming to recruit, in total? (Q8)	The nine studies summarized here with recruitment after 2005 attempted to recruit more than 98,500 subjects.
How many subjects were actually recruited? (Q9)	16 of the 20 studies provided recruitment numbers, and they reported recruiting 84,700 subjects.
Did the consent form allow for future genetic studies of outcomes, in addition to the immediate outcome of interest? (Q26)	11 of the 20 studies reported that the original consent allowed for use of the sample in future genetic studies.
Does your study or repository include patients who have been diagnosed with breast cancer? (Q34)	11 of the 20 studies included breast cancer patients.
Where are the specimens stored? (Q35)	Of the 11 studies that included breast cancer patients, five stored specimens on-site, five off-site, and one was unknown.
How are DNA specimens stored? (Q36)	Five sites reported storing frozen DNA specimens. There was no response from the other sites.
What are the IRB requirements for using the specimens? (Q40)	Six studies reported that future studies of other diseases would be permitted. None of the studies reported that findings were communicated to subjects. Five studies reported that specimens can be sent to other labs for analysis.

Type of specimen collected (Q41)

	Saliva	Whole Blood	Serum	Plasma	Buffy Coat	Hair	Urine	Tumor	Immortalized cell lines	Other
N	2	6	7	3	3	0	1	2	0	3

Task 2: We collected data on past bio-specimen studies

Deliverable 1: Catalog of study manuals and forms for bio-specimen studies

Deliverable 2: Assessment of success of different recruitment procedures

Method: To document successful strategies for specimen collection performed at CRN sites, we surveyed investigators at participating sites to identify past and current studies that have been, or are being, conducted at each institution (see survey instruments in Appendix 1). We identified 33 past or current studies at CRN sites that included specimen collection as part of protocols, of which 20 studies returned the survey (Table 3).

Key Findings:

- There are tradeoffs among recruitment yield, cost, recruitment effort, and burden of participation (Table 4).
    1. Level of recruitment effort is inversely proportional to the response rate. Possible explanations for this phenomenon:
        a. Studies with low response rates increased recruitment efforts in an attempt to reach their targets.
        b. In anticipation of low response rates, researchers may have implemented more recruitment strategies and put effort into community engagement.
        c. In-person invitations may be particularly successful
        d. The incentive is higher in studies with a lower response rate, but a higher incentive may be necessary to encourage participation in studies with a large number of visits (>10) required.
    2. Response rate decreases when participation burden is higher.
        a. If length of visits and/or number of visits is high, burden of participation may be increased.
        b. Sending patients to a collection facility may substantially increase the burden of participation and reduce response rates compared with collection at a routine visit, at home, or by mail.
        c. A large number of activities (e.g., consent, questionnaire, vital measurements, specimen collection, multiple specimens) may increase the burden of participation and reduce response rates.

Table 3. Survey Results Summary

Site	Number of Invitations Sent	Number of Surveys Returned	Number of Extra Surveys	Number Declined to Respond
KPNW	8	6		2
MFRC	7	4		3[1]
KPNC	5	1		4
GHC	5	4	1	1
KPCO	4	1	1	3
HPHC	2	1		1[2]
KPG	1	1		0
HFHS	1	0		1[3]
	33	18	20	15
% Received		55%	61%	

[1]One respondent was not comfortable completing the survey
[2]Survey for the same study was sent to another site
[3]Declined to respond to survey, but did agree to share specimens for breast cancer patients

Table 4. Which recruitment strategies are most successful for collecting specimens?

Level of Recruitment Effort					Burden of Participation				
Response Rate	Number of Recruitment Strategies Used	In-person Invitation	Number of Community Engagement Activities	Reimbursement/ Incentive	Specimen Collection at Facility	Specimen Collection at routine visit, home, by mail	Number of Activities During Visit	Length of Visit	Number of Visits
<11%	3	Y	2	No	Y	Y	3	1 hour	1
<11%	5		3	$25	Y		6	45 minutes	13
<11%	5		3	$25			6	45 minutes	11
11-25%	2		1	$30	Y		5	1 hour	1
26-50%	7	Y	4	$30		Y	4	30 minutes	1
26-50%	2		0	No			4	2 hours	2X/yr
51-75%	2		0	$25		Y	6	1.5 hours	1
91-100%	2	Y	0			Y	2	30 minutes	1
91-100%	2	Y	0	No	Y		2	30 minutes	1
UK	1		1	No	Y		7	3-4 hours	9
UK	2	Y	0	No	Y	Y	3	20 minutes	3
UK	1		0	No		Y	3	25-35 minutes	1
UK	2	Y	0	No		Y	5	5-15 minutes	0
UK	5	Y	0	$120		Y	3	90 minutes	2-14
UK	1		1	No	Y		1	NA	NA
UK	4	Y	0		Y	Y	5	4 hours	1
UK	2		0	$30/$50		Y	4		
UK	1		0	$600			5		21
UK	1		2	$250			6	1 hour	5

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Task 3: We assessed feasibility of recruitment procedures at each study site

Deliverable: Identification of potential barriers to new specimen collection.

Method: We present several examples to illustrate potential barriers to new specimen collection.

Example I: Barriers to using specimens in existing repositories at PMRP

The Marshfield Clinic Personalized Medicine Research Project (PMRP) is a population-based biobank with samples from approximately 20,000 adult participants. Opportunities for genetic research are limited only by the sample size of 20,000 which may be too small to conduct research on rare cancers. Subjects have actively consented to allow access to their medical records, and they have provided a blood sample for DNA, plasma, and serum extraction. They also completed detailed dietary histories and physical activity questionnaires. A waiver of written informed consent allows for access to stored pathology samples for PMRP subjects. Greater than 99% of subjects consented to be recontacted for future studies and approximately 2/3 hypothetically agreed to participate when recontacted.

Procedures to access the biorepository have been established and are available on the study website, along with a detailed methods paper and all study forms **(**www.marshfieldclinic.org/pmrp**)**. In brief, approvals are required at three levels: 1) scientific merit, 2) IRB, and 3) Oversight Committee. Subjects gave written informed consent to allow their deidentified samples and data to be sent off-site to external collaborators. This event would require a Data and/or Material Transfer Agreement with the collaborating institution. Funding is required to conduct necessary bioinformatics for identifying samples and for the lab staff to pull samples. These procedures are well developed and have been implemented numerous times. The only potential barrier at this site is time. Several months are required to complete various approvals and for PMRP staff to identify and pull samples. After a study has been completed, all data gathered must be added to the PMRP database and any residual samples must be returned to the biobank.

Key Findings:

- Barriers to using specimens in existing repository at MCRF. Well established policies and procedures are in place, and the following steps must be taken prior to specimen use:
  1. Evaluation of scientific merit
  2. Funding
  3. IRB approval
  4. Oversight committee to review application
  5. Evaluation of quantity of material requested

Example II: Barriers to using specimens in existing tumor repository at PMRP

Clinical pathology samples are retained for 25 years at the Marshfield Clinic. Blocks and slides are available. Approval to use the samples must be obtained from the Marshfield Clinic IRB. There are currently no written procedure manuals for accessing samples and this has occurred on an ad-hoc basis in the past. There are two barriers to accessing these samples: 1) the availability of older samples is not recorded

electronically and is available only in hand-written logs, and 2) limited availability of pathologists and technicians to review and obtain samples for research. Because there is no set process, access to samples for research is established on a case-by-case basis. Samples have been accessed for research in the past and deidentified samples have been shipped off-site. A signed Material Transfer Agreement is required prior to sending any samples off-site.

Key Findings:

- Barriers to using specimens in existing tumor repository at MCRF:
  1. No electronic indicator of specimen availability.
  2. Limited availability of pathologist/technician time to find block, pull block, cut slides, etc.
  3. Lack of standard policies creates confusion about what steps are needed to access specimens.

Example III: Opt-in vs. opt-out model of consent for repositories

There are two models of consent for repositories – opt-in and opt-out. Opt-in requires action for inclusion (e.g., a signed consent form for participation). Without consent, a potential participant would be excluded from the repository. Opt-out models require action for exclusion (e.g., a signed letter requesting to not be included). If a participant does not opt-out, they will be included in the repository.

The opt-out model of consent offers some advantages over the more traditional opt-in model of consent. Participation rates are higher, samples are more likely to be representative of the population and to accrue much faster, and less time and money is required for obtaining consent. In contrast, opt-in models are more likely to ensure participant understanding of implications of the research and offers a chance for participants to provide explicit consent. Additionally, the opt-in model of consent allows for broad data collection.

When an opt-out model of consent is used for a repository, samples are typically de-identified to prevent samples being linked up with the medical record. Several barriers to this approach are as follows:

1. If the medical records employ a date shifting technology, events tied to specific dates (e.g., studies of seasonal allergies) cannot be evaluated.
2. If specific alleles linked to a disease are discovered in a completely de-identified sample, there is no way to inform the patients who have contributed those samples.
3. Because there is no ability to identify patients for re-contact to acquire additional samples, the collection of serum samples for proteomic analysis is not possible.

With both models of consent, technical, organizational, and legal safeguards should be shared with participants. These safeguards should include transparent rules regarding access to medical records, mechanisms of complaint, and understandable information about the research. Laws regarding use of specimens are frequently evolving (e.g., pre-2005 samples don't need consent, while post-2005 samples do need consent) and vary from state to state. When consent is not appropriately addressed in the planning phases, legal action can result. For instance:

- In March of 2009, the Texas Department of State Health Services was sued over keeping newborn blood spots (NBS) without consent. As a result, Texas is adopting an opt-out approach for NBS storage and use.

- In June of 2009, the State of Minnesota and the Minnesota Department of Public Health were sued over failing to comply with the Minnesota Genetic Privacy Act (MGPA) and continuing to store and use NBS without consent (violation of MGPA, 8 tort claims, fundamental rights claims, government taking).

Key Findings:

- Barriers to the opt-out model of consent for repositories include:
  1. Degree of 'scrubbing' required means that physician notes are not sufficient to extract information for some phenotypes, e.g., on cataracts.
  2. De-identification process removes the ability to go back and re-contact subjects for additional information. The medical record becomes the only source of phenotypic information.
  3. There have been some lawsuits surrounding the models of consent for newborn screening programs in Minnesota and Texas.

Example IV: Barriers to specimen collection for sites without existing infrastructure to collect/store specimens

Several CRN sites do not routinely collect biospecimens for biobanking and research purposes. There are significant barriers for developing a biospecimen repository. They include:

1. buy-in of stakeholders and senior leadership,
2. significant start-up costs, and
3. sufficient physical space for specimen storage.

One of the first steps in establishing a biorepository is obtaining support from senior leadership and other stake-holders. It may be desirable to hold seminars as well as smaller meetings to inform key personnel of the costs and benefits of establishing a biorepository. It may also be helpful to survey health plan members to understand concerns, particularly around privacy, and to identify barriers to participation. Outreach by way of seminars or newsletters may be useful in generating support for a biorepository from health plan members.

There are several options for establishing a biorepository, each come with a different set of costs and benefits. A biorepository could be established and managed on site, samples could be sent to an existing biorepository, or a commercial biobank could be used to process and store samples.

An on site repository would require a dedicated physical space and research staff to manage the repository. Minimum equipment would include a computer, sample processing equipment and space, refrigeration, freezers, and liquid nitrogen tanks. A number of security measures would need to be installed both to prevent unauthorized access and to protect sample integrity (e.g. monitors and alarms for the liquid nitrogen). The benefits of an onsite repository include complete control and easy access to samples. However, like any resource, there will be time and costs involved with managing and maintaining the space.

An attractive option for biobanking samples is collaborating with an existing biorepository. For example, most universities routinely store samples and it may be possible to contract with a local medical center or university for sample storage. This would eliminate the need for finding space and qualified staff, which

could be a cost savings. The disadvantages of this option include the need to transport specimens, and the lack of control regarding staff qualifications and sample safe guards. Accessing samples in a timely manner may be more difficult at an offsite location. Finally, sample ownership must be clearly stated prior to any sample storage agreements, and the conditions of potential collaborations must be carefully outlined.

A third option for biobanking is to contract with a commercial biobank. This would likely be more expensive than collaborating with a local medical center or university. However, commercial biobanks offer state-of-the-art sample processing, sample storage, security and tracking systems. Shipping samples to and from a commercial biorepository is usually quite easy because they are familiar with interstate shipping regulations, and samples can be retrieved in a timely manner. When using a commercial biobank, sample ownership and use is not questioned as it could be if storing samples in a research lab at a university. One drawback to utilizing a commercial biobank is if the facility decides it is no longer feasible to continue operations. In 2009, the national biobank facility run by OnCore in the UK decided to cease functioning as a biobank; as a result, the facility must dispose of the samples. In this case, they are soliciting applications to send the samples for approved biomedical research. However, this possibility speaks to the need for specific contract language indicating sample ownership and handling should the facility close.

Of prime importance for any storage option is careful tracking of specimens – both the initial sample as well as "daughter" vials (sub-aliquots). Samples should be barcoded and tracked with software customized to each system and needs.

Also, preferably before any samples are collected, a committee should be established to develop guidelines for use of biospecimens, including how (or if) outside scientists can access the samples, protection of patient privacy and how patients can "opt-out" or request that their sample be destroyed, sample handling, how long specimens will be kept, and how samples will be destroyed.

Key Findings:

- Barriers to specimen collection for sites without existing infrastructure to collect/store specimens:
  1. At some sites there is a lack of freezer/storage capacity.
  2. There are substantial barriers to start-up, including obtaining and possibly renovating space to meet biosafety requirements, and costs including staff training and/or hiring, equipment.
  3. A key barrier is the need for buy-in of stakeholders including IRB and senior management, and the need for commitment and access to internal funding sources, since this infrastructure is unlikely to be funded completely by external sources.
  4. An alternative is to collaborate with other institutions (e.g., universities or other CRN sites) that have the capacity to store, process, and maintain specimens, However, this requires establishing good collaborative relationships and trust between institutional partners.

Example V: Barriers to specimen collection through established clinical laboratories

KPNW is currently implementing a procedure to access clinically-derived blood specimens for research. The NW Biobank is planned as a population-based biobank with a targeted sample size of 100,000 people. The planned procedure to collect samples is as follows: Members will be consented through the mail, prior

to the point-of-care where their blood will be drawn; Following consent, after a blood draw for any reason, the blood will be sent to our centralized blood processing facility at the regional Airport Way Laboratory (AWL); Any blood that remains after clinical testing is completed will be set aside and retained for research.

Over the entire adult KPNW membership, about 60% will have at least one blood draw within a three-year period of time; as many as 80% of members with cancer, cardiovascular disease, and diabetes may receive a blood draw in that time.

Although the proposed approach presents some logistical challenges, the primary barrier to implementation is funding. This approach requires close collaboration and communication with clinical staff at the regional laboratory. A key element of our success has been the support and buy-in of a manager within the AWL facility who is able to make decisions, commit resources, and is well informed about the informatics and operations of the facility. A second key element is the level of automation in the AWL facility. The barcoding and specimen tracking system will facilitate the process of identifying specimens for members who have consented and retaining those specimens for research. Programming in the laboratory informatics systems was necessary, as was establishing a secure procedure to update lists on a daily basis from the research center to the AWL facility as new members consent to participate in the biobank.

The specimens themselves also pose some limitations. The laboratory standard procedure was to retain specimens for seven days after collection in case the sample needed to be re-run. We have since negotiated with the laboratory staff to reduce this retention time to 2 days since, according to their own policies, they do not re-run samples after 48 hours. The retention time is important for the sample quality and overall yield, which declines over time depending on the stability of the analyte. Although DNA is stable over 48 hours, RNA and certain proteins may not be stable, limiting the utility of the collection for certain uses. Another issue is the overall volume of blood. Typically only 2.5 to 3 ml of blood remains following clinical testing. Although this is sufficient for current DNA-based technologies, it is limiting for other procedures. A possible solution is to collect more than one blood specimen from each subject. A large portion of members will have multiple blood draws within a short (e.g., three years) period of time.

Another consideration with the proposed approach is the bias inherent in who gets a blood draw for clinical purposes. For example, this would be a very poor approach if one is interested in collecting specimens on children, since typically < 10% of the pediatric population has a clinical blood draw within a three year period of time. Certain healthy adult populations, such as young men, do not tend to get blood drawn. In fact, over all age groups, males tend to have blood drawn less frequently than females. Thus, the overall cohort may not be representative of the entire membership. However, through the VDW we can describe the differences between the biobank cohort and the entire membership. In addition, it may be possible to target blood collection for certain under-represented populations if this is deemed important to a particular research question. Although this approach will work fairly well across a large number of subjects, if a specimen is required from a specific individual it may take some time for that person to have a clinical blood draw. Thus, this approach will work best over a large patient base.

Key Findings:

- Barriers to specimen collection through established clinical laboratories:
  1. It is critical to obtain buy-in of management from regional clinical laboratory

2. This approach depends on the available clinical infrastructure including a regional laboratory and a certain level of automation at the regional laboratory.
3. There is a bias in who gets a clinical blood draw, which may limit the utility of the collection for some purposes.
4. The stability of analytes of interest is critical, since specimens are only available after they are no longer useful for clinical purposes.

Task 4: Development of Study Documents

Deliverable: Manual of best practices for the acquisition of specimens across the HMORN

Methods: We assembled best practices guidelines from existing professional organizations and created example study documents to guide future CRN research studies that propose specimen collection (see Appendix 7). This documentation can be used to guide future genomic research.

Key Findings:

- Based on current technologies, we recommend that two types of specimens should be collected to facilitate future CRN genomic studies: saliva or blood (Table 5).
- We developed draft recruitment materials including an invitation letter, informed consent documents for both blood and saliva specimen collection, a questionnaire, and an abstraction form. (see Appendix 2 & 3). **These documents can serve as examples for future CRN studies that require specimen collection.**
- We developed budget estimates for both blood and buccal cell specimen collection (Table 6). The majority of costs are personnel expenses; there is not a significant difference between the two types of specimen collection, with blood collection costing about $1020 per sample, and saliva costing about $956 per sample. The above estimates assume that the personnel effort is the same for both blood and saliva collection (see Appendix 4) because costs are primarily associated with tasks related to administrative responsibilities (e.g., IRB, compliance), identification of the study population, and recruitment, and not for tasks specifically related to handling the specimens. However, there was some disagreement in our group about this assumption. As this assumption changes (e.g., lower personnel effort required for saliva collection than for blood collection), then saliva collection becomes a more cost effective approach. **These budget estimates can inform future CRN studies about the relative costs of each type of specimen collection.**

TABLE 5. OPTIONS FOR FUTURE SPECIMEN COLLECTION

	Method	Advantages	Limitations
Existing Biobanks	A biobank is a collection of human specimens and associated data for research purposes, the physical structure where the specimens are stored, and all relevant processes and policies. This may include extracted DNA, transformed cell lines, frozen blood or other tissue, or biological materials for use in future DNA analysis.	The samples and data are already available and the cost to access them should be reasonable and much lower than collecting samples de novo.	1) existing written informed consent documents may not allow for data and sample sharing outside the local institutions; 2) subjects may not be able to be re-contacted (because death, refusal or inability as stated in the consent form) for additional information, such as standardized questionnaires; and 3) samples may not be stored optimally for future use (such as FFPE tumor tissues).
Buccal Cells	Two protocols could be considered: (1) mouthwash collection and (2) the Oragene collection kit. Mouthwash collection requires participants to swish mouthwash around their mouth and then spit into a collection cup. The collection cup can be mailed to a laboratory, and the cells can be stored in liquid nitrogen. To collect DNA with the Oragene kit, the participant spits directly into the collection container, seals, and shakes the container. The containers can be mailed to the laboratory, and stored at room temperature long-term. The quality and yield of DNA from the Oragene kits may be superior to other buccal cell collection methods, and we recommend Oragene as the preferred method for collection of buccal cells at this time.	Buccal cells are easy to collect and DNA from various buccal cell collection methods are being used routinely for genome-wide scans. Advantages of using buccal cells as a source of DNA include the non-invasive nature of sample collection that is generally more acceptable to study participants, and the ability to collect samples via the mail instead of a clinical visit. There may be lower storage costs compared to DNA collected from whole blood if the samples are only stored for a few years at room temperature. The costs of storing frozen aliquots would not differ.	The disadvantages include the variability in sample yield and quality. DNA from buccal cell collections may be of lower quality that DNA from blood, and the yield is lower. However, the low yield can be overcome by collecting multiple samples, since collection is relatively inexpensive and easy.
Blood Samples	Typically the method to collect blood is venipuncture, which, although invasive, is relatively low risk and typically well tolerated. Finger-puncture to collect blood samples that are subsequently collected as dried samples on DNA-cards is another means that is well accepted by patients.	Collecting DNA from venipuncture holds specific advantages, namely: (i) higher volume of DNA, (ii) quality of specimen (i.e., highly unlikely to be contaminated with foreign DNA), and (iii) source certainty (having the patient present at the time of collection adds assurance that the DNA is from that person). Blood and/or its DNA can be stored in different ways: (1) whole blood preserved as dried blood spots; (2) isolated genomic DNA, (3) immortalized lymphocytes from whole blood or separated lymphocytes, prepared immediately or subsequent to cryopreservation.	Considerations for blood collection include the processing required (aliquoting and extracting DNA), and the storage requirements (DNA is stored at -20^{o}C and whole blood is stored at -80^{o}C). While venipuncture is relatively well tolerated, some studies point to this being the main reason for recruitment refusal. Another reason for refusal is when venipuncture requires a separate visit to a research clinic. Otherwise compliant research subjects balk at the time and effort to make a special clinic visit, even in the face of an incentive. Blood collection has high cost relative to other mechanisms.

Table 6. Budget Estimates for Specimen Collection

BUDGET MODEL OUTLINE

Assumptions: The goal is to obtain 100 biospecimens. We assume that we will have a 20% response rate, so we will need to mail invitations to 500 people (x2 for follow-up reminder mailing). For saliva collection, we assume initially that 150 will respond, but only 100 will complete the entire process. We will send $10 with the saliva collection kit as an incentive, and an additional $25 if they return it. For the blood collection, the participants will receive the entire $35 incentive when they come in for a blood draw.

Start Date: July, 2010

Costs for both approaches:

PI . . . . . 10% FTE
Programmer. . . . . 20% FTE
Project manager . . . . . 10% FTE
Research assistant . . . . . 25% FTE

Printing materials (n = 1000) $200
Postage (500 @ $ .44) x 2 mailings $420

Total $88,000

Costs specific to blood collection:

Phlebotomist . . . . . 5% FTE
Lab technician . . . . . 5% FTE
Medical supplies for 100 blood draws (@ $20 each). $2000
Shipping (once per week for 20 weeks)
- Dry ice . . . . . $31 x 20 = $620
- Container . . . . . $75 x 20 = $1500
- Overnight shipping . . . . . $60 x 20 = $1200

Freezer (*only for sites without existing freezer space). . . $7000
Incentives: . . . . . 100 @ $35 each = $3500

Total $14,500

Costs specific to saliva collection

Oragene Kits (150 @ $20 each) $3000
Postage (for kits—150 @ $3 each) $450
Shipping (to central location) . . . . . $135 x 1 = $135
Incentives: . . . . . 150 @ $10 each = $1500
. . . . . 100 @ $25 each = $2500

Total $7,585

Appendix 1: Survey

The HMO CRN Cancer Research Network

CRN Pharmacovigilance Study—Genomics Working Group Survey

Instructions

On the form below, please identify a minimum of **five** studies or repositories (and corresponding study personnel) that collect/collected biological specimens from research subjects at your site. The PIs and/or contact people identified will be sent a follow up survey that explores recruitment strategies and the current status of the biological specimens. Please list a contact person for each study/repository who is **highly knowledgeable** about the study/repository.

This survey is not intended to be an exhaustive list of all studies at your site. We prefer a more targeted approach, using the following criteria to describe a qualifying study or repository:

Inclusion Criteria

- Specimens were collected within the last 5-10 years or are currently ongoing
- Specimens were collected from which DNA could be extracted (i.e., ideally we want blood, saliva, or fresh/frozen tumors)
- Specimens are still accessible by investigators at your site

If your site has many studies or repositories to choose from, and you must select a subset to respond, we have the following preferences:

Preferences (in order):

- Studies or repositories with specimens that are still available for use in future research
- Studies or repositories that collected specimens from patients with breast cancer
- Studies or repositories that collected specimens from patients with other types of cancer
- Studies or repositories that collected specimens for genetic/genomic questions
- PI is still available to answer questions
- Studies or repositories with a large sample size (versus pilot studies)
- Studies or repositories that were not industry sponsored

Notes: Repositories can include specimen collections for research purposes or clinical collections (e.g., tumor repository in pathology department).

If there are not five eligible studies or repositories at your site, please complete the form for as many as possible.

Please return this form by next **Tuesday, January 20th.**

The CRN Pharmacovigilance Genomics Working Group

Form should be filled out by the CRN Pharmacovigilance Site PI or their representative

Please list the studies, biorepositories, and clinical collections that you are aware of at your site that have collected biological specimens (e.g., blood, tumor, saliva). We are especially interested in studies or collections that might include patients with breast cancer, although this is not necessary.

Note: This survey is provided as a Microsoft Word form. The document has been locked, limiting access to the gray-shaded areas only. You may tab between fields, or use your mouse to click into each field. It is fine if information (e-mail address etc.) wraps within each cell. If you need to provide additional information, please use the additional information field.

Respondent Information

Name:	Email:	Telephone:	Name of HMO:

Name of Study, Biorepository, or Clinical collection	Name of PI	Contact Person	Phone Number	Email Address

Additional information (if necessary):

Biorepositories: Can include specimen collections for research purposes or clinical collections (e.g., tumor repository in pathology department).
Clinical collections: Specimens collected as part of clinical care, e.g., tumor blocks held by pathology.

Please return the form to Joanna.E.Bulkley@kpchr.org or fax to: 503.335.2428, Attn: Joanna Bulkley.

The CRN Pharmacovigilance Genomics Working Group

CRN Pharmacovigilance Study—Genomics Working Group Survey

Instructions

The CRN supplemental study of Cardiotoxicity following Herceptin Use among Women with Invasive Breast Cancer is seeking to identify and learn about collections of biological specimens from women with breast cancer. The research aim is to identify genetic risk factors that influence whether or not a patient will experience cardiotoxicity as an adverse effect of treatment with Herceptin among patients with breast cancer. This survey is designed to learn about recruitment strategies and methods that have been used in completed or ongoing studies in which biospecimens were, or are being, collected.

Second, we are trying to identify samples from breast cancer patients, regardless of whether they were collected for a breast cancer study or not. For example, one study conducted at KPNW had 20,000 participants. Some of these participants had breast cancer (~400), although the purpose was to study hereditary hemochromatosis.

This form should be filled out by someone very familiar with the study or repository. If you were asked to complete the survey for more than one study or repository, please use a separate copy of this form for each.

Please return the form to Eresha.F.Bluth@kpchr.org or fax to: 503.335.6311, Attn: Eresha Bluth.
Please return the form within the next two weeks.

Note: This survey is provided as a Microsoft Word form. The document has been locked, limiting access to the gray-shaded areas only. You may tab between fields, or use your mouse to click into each field. f you ever find your answer is limited by the space available, please type any additional information in at the end of the form where a space has been provided for that purpose.

Survey Respondent Information

Name:
Email:
Telephone:
Name of HMO:
Role:
PI (if other than you):

If more than one respondent completes this form, please enter information on second respondent at end of survey.

Study or Repository Identification

1. What is the Name and Acronym of the study or repository? (Limited to 150 characters)

2. What are/were the specific aims of the study? (Please be brief—limited to 2000 characters)

3. During what time frame did recruitment take place?

4. Is the study or repository still open to recruitment? (Click this box to choose from the list)

5. Do you maintain a study or repository website? (Click this box to choose from the list)
   If **YES**, please provide URL:

6. What was the study design? (Check all that apply)
   - Cohort ☐ 1 00
   - Case control ☐ 2
   - Clinical trial ☐ 3
   - Family-based ☐ 4
   - Drug dosing ☐ 5
   - Other, please state ☐ 6

7. Were genetics or genomics questions a primary or secondary focus of the research? (Click this box to choose from the list)

Who Was Recruited for this Study or Repository?

8. How many subjects were you attempting to recruit?

9. How many subjects were actually recruited?

10. What were the inclusion/exclusion criteria for patients recruited into this study or repository?
    Inclusion criteria
    Exclusion criteria

11. Did you attempt to recruit certain subsets of the population?
    (Please check all that apply)
    - Minorities—please list which one(s) ☐ 1 00
    - Rural residents ☐ 2
    - Inner-city ☐ 3

12. Were children included? (Click this box to choose from the list)
    If **YES**, from what age?
    How did you handle reconsent when they turned 18?

13. Did you include vulnerable populations? *(Check all that apply)*

Institutionalized individuals	☐ 1	00
Pregnant women	☐ 2	
Fetuses	☐ 3	
Employees	☐ 4	
Decisionally/cognitively impaired	☐ 5	
Economically disadvantaged	☐ 6	
Educationally disadvantaged	☐ 7	
Non-English speaking populations	☐ 8	
Elderly (≥ 85 years)	☐ 9	
Prisoners	☐ 10	

14. What method was used for the initial contact with the participant?

(Check all that apply)

Posted flyers/posters	☐ 1	00
Advertisement in local/national media	☐ 2	
In-person invitation by research staff	☐ 3	
Study specific website	☐ 4	
Email invitation	☐ 5	
In-person invitation by clinic staff (e.g., their physician)	☐ 6	
Phone call	☐ 7	
Mailed invitation	☐ 8	
Other	☐ 9	

15. Were any community engagement or consultation activities used to inform the eligible population about the project? *(Check all that apply)*

Study Newsletter	☐ 1	00
Informational Brochure	☐ 2	
Media Interviews	☐ 3	
Community presentations to a lay audience	☐ 4	
Study video	☐ 5	
Other:	☐ 6	

16. Did you use group/community consent? (e.g. researchers working with groups/tribes sometimes get consent from community leaders as well as individual participants)

(Click this box to choose from the list)

If **YES**, what group/community was involved:

Briefly describe the group/community consent process:

17. What was the overall response rate? Please answer either or both of the questions below, as appropriate.

17a. Response rate = the number of participants divided by the number of eligible people. (Click this box to choose the best option)

17b. Response rate = the number of participants divided by the number of eligible people **contacted**. (Click this box to choose the best option)

18. Did the response rate depend on any of the following characteristics?

Characteristic	**Yes/No/Not Applicable**	**If YES, the response rate was highest for...**
Sex	(Click this box to choose from the list)	(Click this box to choose from the list)
Age Category	(Click this box to choose from the list)	Ages to
Case/Control Status	(Click this box to choose from the list)	(Click this box to choose from the list)
Race/Ethnicity	(Click this box to choose from the list)	Racial/Ethnic group:
Other known characteristic	(Click this box to choose from the list)	Category:

19. Where was the biological specimen collected? *(Check all that apply)*

The patient was sent to a collection facility at a central site ☐ 1 00
The patient was sent to a collection facility at one of multiple sites ☐ 2
The specimen was collected during a visit in the patient's own home ☐ 3
The specimen was collected during a routine clinical/hospital visit ☐ 4
A collection kit was sent through the mail ☐ 5
Other (specify) ☐ 6

20. This question refers to alternatives you may or may not have offered study participants. If you collected blood in your study or repository, did you offer participants who initially refused an alternative method of specimen collection (e.g., saliva or cheek swab)?

NO, we did not collect blood ☐ 1 00
NO, we did collect blood, but we did not offer an alternative ☐ 2
YES. If YES: What proportion of participants who initially refused the blood draw agreed to participate after offering the alternative method? ☐ 3

(Click this box to choose the best option)

What was involved in participation in this Study or Repository?

21. What information did you collect at the time of enrollment?
(Check all that apply)

- Informed Consent ☐ 1 00
- Questionnaires/Surveys (If YES, please provide a copy) ☐ 2
- Vital statistics and anthropometry (e.g., height, weight, blood pressure) ☐ 3
- Sputum/buccal smear only ☐ 4
- Blood ☐ 5
- Multiple blood samples ☐ 6

Other specimens (tumor tissue, etc.) removed as part of clinical surgical procedure (List:)

Other specimens as part of procedure specifically for research protocol (List:)

Any other information (List:)

22. Approximately how long did the average research visit last?

23. How many visits were required in the research protocol?

24. Did you reimburse participants? (Click this box to choose from the list)
If **YES**:
Monetary reimbursement: How much/how often?
Non-monetary: What was offered/how often?

25. Did you provide any other sort of an incentive to study subjects? (Click this box to choose from the list)
If **YES**, please describe:

26. Did the consent form allow for future genetic studies of outcomes other than the immediate outcome of interest?

- **Yes**, for undisclosed number/type of tests (open use) ☐ 1 00
- **Yes**, but only for specific tests/uses (conditional use) ☐ 2
- **Yes**, but patient would be contacted for consent to additional use ☐ 3
- **No**, it was explicit that samples were only tested as specified in the consent ☐ 4

27. Do you have a methods paper or study manual that you could share with us? (Click this box to choose from the list)
If **YES**, please provide a copy or a reference:

28. Is there a systematic policy or process to access previously collected clinical or research specimens at your institution? (Click this box to choose from the list)
If **YES**, please provide a copy or a reference:

29. Has your institution developed general policies or procedures for the collection and use of specimens for research purposes? (Click this box to choose from the list)
If **YES**, please attach written documentation of these procedures if possible.

30. Is there any other information we should know about your experience collecting specimens? (e.g., what types of studies performed the best? What were the biggest challenges?)

31. What were some of the biggest challenges you faced?

IRB issues, such as getting consent form approved ☐ 1 00
Budgetary, such as getting funding from NIH or elsewhere ☐ 2
Participation, such as potential participants concerns over privacy or health insurance ☐ 3
Analytic, such as getting necessary genetic biostatistical expertise to help analyze data ☐ 4
Other; specify: ☐ 5

32. If you could do one thing over, what would that be?

33. What is the one thing that you are glad that you **did** do?

We would like to identify examples of study documents to guide our development of future recruitment and specimen collection strategies for the CRN Pharmacovigilance Study. If possible, **please provide us with a copy of relevant study documents** (e.g., recruitment materials, consent form, abstraction form, information materials used as part of recruitment, flyer). You can provide these documents using email or fax by following the instructions on the first page of this survey. Any documents that you share will be circulated among the Genomics Working Group for informational purposes.

34. Does your study or repository include patients who have been diagnosed with breast cancer?

No ☐ 1 00
Yes, PLEASE CONTINUE WITH THE SURVEY ☐ 2

Please continue with the survey ONLY if you responded 'YES' to the previous question. Please answer the following questions as best you can, referring to the patients with breast cancer.

35. Where are specimens stored? (Click this box to choose the best option)

36. How are DNA specimens stored (Click this box to choose from the list)
If FROZEN, please state temperature: degrees

37. Is this project part of a multi-site study? (Click this box to choose from the list)
If YES, please state how many other sites:

38. Are/will specimens go to a NIH repository? (Click this box to choose from the list)
If YES, please state which repository:

39. Are/will associated data go to a NIH repository? (Click this box to choose from the list)
If YES, please state which repository

40. What are the IRB requirements for using the specimens?
(Check all that apply)
Future studies of other diseases are permitted ☐ 1 00
Data are returned to subjects ☐ 2
Specimens can be sent to other labs for analysis ☐ 3

41. Type of specimen collected *(Check all that apply)*
Saliva ☐ 1 00
Whole blood ☐ 2
Serum ☐ 3
Plasma ☐ 4
Buffy coat ☐ 5
Hair ☐ 6
Urine ☐ 7
Tumor ☐ 8
Immortalized cell lines ☐ 9
Other pathology samples ☐ 10
Other, please state ☐ 11

42. Status of study or repository (Click this box to choose from the list)
If you HAVE NOT STARTED RECRUITMENT, projected start date:

If there was any question in the survey for which the answers options or text box was too limited, please type your additional information here:

If more than one respondent participated in completing this survey, please include their information here. Please include name, email, telephone, HMO affiliation, role, & PI name.

We may contact you at a later time to clarify your responses.

Thank you very much for your time and effort!

Appendix 2:
Draft Recruitment Materials—
Consent Form

SITE NAME

CONSENT TO PARTICIPATE IN A MEDICAL RESEARCH STUDY

FORMAL TITLE: *Title (Protocol #)*

You are being invited to participate in a research study being conducted by researchers from SITE NAME. To decide whether or not you want to be part of this research, you should understand the risks and benefits in order to make an informed decision. You have the right to know what the purpose of the study is, how subjects are selected, what procedures will be used, what the potential risks and benefits are and what is expected of you as a study participant. This process is called "informed consent." This consent form gives information about the research study, which your study doctor will discuss with you. You will be asked to carefully read this consent form and discuss anything that you do not understand with your study doctor or staff. Once you understand the study, you will be asked to sign and date this consent if you choose to participate. You will be given a copy of the signed and dated consent form.

STUDY PURPOSE AND BACKGROUND

You are being invited to participate in a medical research study being conducted by researchers from SITE.

The purpose of this study is to understand why some women experience side-effects from some chemotherapy that is given to treat cancer. These side-effects can be harmful, including damage to your heart, which can lead to cardiovascular disease. We would like to find ways to identify women before they start treatment. Specifically, we would like to identify women who can benefit from the chemotherapy without experiencing these harmful side-effects, or to identify women who will experience side-effects and could consider alternative therapies instead. A person's unique genetic make-up could provide some clues to help us understand how individuals will react to these drugs. Please read this information before deciding whether or not to participate in this study.

The (blood/saliva) sample you provide will be frozen and stored for future analyses of genetic and biologic (if blood) markers of disease. No analysis will be done without appropriate scientific review. In order to protect your privacy, your sample will be assigned an identification code that does not include any of your personal information. Your sample will be stored for as long as it is useful, unless you ask us to destroy it sooner.

We are inviting several thousand women from health maintenance organizations (HMOs) across the country to participate in this research study, with (site#) to be enrolled at SITE. You are being asked to participate in this study because you have been identified as a woman over 18 years of age who has been diagnosed with breast cancer.

This study is funded by (Funding Agency)

STUDY PROCEDURES

If you decide to participate, you will be asked to . . .

- Contribute a (blood/saliva) sample to research.
- Complete a study questionnaire.
- Give permission to use and connect your blood sample with health information from your medical record, pathology specimens, or other information collected by (HMO).
- Allow approved researchers to contact you for future studies that need more information. You decide whether or not to take part in any future studies.
- Choose whether or not your data can be posted in a US government database that can be broadly shared with researchers worldwide to maximize the chances of new discoveries. The use of data posted in this database may occur without approval by a committee responsible for research subject protection and without the knowledge of this research team. This is the only time unapproved research is permitted.

Why do we want to store your blood and health information?

Genes have a role in many common diseases. Even subtle genetic differences between people may change how people respond to treatment. A sample from thousands of people is needed to discover these genes. This project is trying to apply genetic science to human health care. Genetic information will be extracted from the stored sample and linked to health information in medical records so scientists can look at how genes are related to health and response to treatment.

How long will I be in the RESEARCH STUDY?

If you decide to contribute to the RESEARCH STUDY, your (blood/saliva) and health information will be stored for an unknown length of time. If you decide now, that your (blood/saliva) and health information can be kept for research, you can change your mind at any time, even if you are no longer a member of YOUR HMO.

Will the results of this project be shared with me?

This research is not intended to benefit individual participants. You will not receive personal results from the RESEARCH STUDY. Research results are not the kind of information that you or your provider would use to make decisions about your current health care. If scientists discover information as a result of this research that is of substantial medical importance to you, we will recontact you and ask if you want to learn the results.

RISKS

There are some risks from drawing blood including bruising, lightheadedness, or infection, although these are unlikely to occur. We will take every precaution to minimize these risks. The biggest risk to you is the unexpected release of your protected health information. The results of your genetic analysis will not be entered into your medical record and will not be shared with you or your family. Also, in accordance with the law, these results will not be released to employers or insurance companies. Any records or material that would identify you will be kept confidential to the extent allowed by federal and state law.

This study may include risks that are unknown at this time.

BENEFITS

Include an equivalent statement to: There are no direct benefits to you for participating in the RESEARCH STUDY. This research may improve how doctors treat breast cancer in the future and help avoid risks of treatment for some women. This study is not designed to treat any illness or to improve your health.

ALTERNATIVES

You may also choose not to contribute your (blood/saliva) to this research study. You may also withdraw from this focus group at any time.

COSTS/PAYMENT

Describe what costs the participant will incur for their participation and what costs will be covered as a part of their Health Plan coverage, as described in their Service Agreement.

The RESEARCH STUDY has no extra costs for you or your insurance company. You will not be charged to participate in this study nor will you receive any money for participating in the RESEARCH STUDY.

INJURY

For studies involving only Kaiser members, state: If you are harmed as a direct result of this study, medical treatment will be provided at no additional cost within the limits of your current existing health care coverage through HMO, as described in Evidence of Coverage. You will not be paid for any other loss as a result of the injury, such as lost wages, pain and suffering.

VOLUNTARY PARTICIPATION/TERMINATION

Participation in the study is completely voluntary. Your decision whether or not to participate in the study will not affect your medical care. If you decide to participate, you are free to change your mind and discontinue participation at any time without any effect on your medical care or eligibility for future care or membership in HMO.

CONFIDENTIALITY

As appropriate, state:

While no one can guarantee absolute confidentiality, the chance that this information would be given to someone who is not approved to see the information is extremely small. Your personal information such as your name and medical number will be removed from the sample. Then the blood sample and your health information will each be given a special code. This code could be linked back to you. However, the code needed to link you and your blood or health information will be kept separate from the sample information and strictly protected. We expect less than a handful of people will have access to the link to the code. All information will be kept in a computer database that is only for research. The computer system is located in a locked and physically secure facility, and it is protected by a state of the art “firewall” from unapproved entry (“hackers”).

Information about you obtained for this study will be kept confidential and will not be released without your written permission unless compelled by law. In certain circumstances, the Food and Drug Administration (FDA), as well as other health authorities or government regulatory agencies, and/or monitors hired by the

study sponsor, *(sponsor name)*, as well as the SITE Institutional Review Board may review your study/ medical records, and might request copies of some documents. However, if copies of your records are requested, information that would reveal your identity (such as your name) will be removed before the copies are provided. Because of the need to release information to these parties, absolute confidentiality cannot be guaranteed. Your identity will not be revealed in any publication or release of study results. If you decide to participate in this study, you will also be giving consent for the medical research investigator or his/her assistants to review your medical records as may be necessary for this study.

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained above. If you agree to allow researchers to post your data in a US government database, the **Certificate of Confidentiality** does not protect your data from being shared with any other federal agency for non-research purposes. Your name and address will not be posted in such a database, although it might be possible for you to be identified by the information that is posted combined with other information.

QUESTIONS

Any study-related questions, problems or injuries should be directed to the physician responsible for the study within HMO, *(physician name)* at *(telephone number)*, or you may call the doctor(s) listed below:

Dr. _____ at _____
(Physician name) (Physician telephone number)

Dr._____ at _____
(Physician name) (Physician telephone number)

Questions about your rights as a study participant, comments or complaints about the study also may be presented to the Institutional Review Board for the Protection of Human Subjects, IRB NAME, ADDRESS, AND PHONE NUMBER.

I have read the above and am satisfied with my understanding of the study, its possible benefits, risks, and alternatives. My questions about the study have been answered. I hereby voluntarily consent to participation in the medical research study as described. I have been offered copies of this consent form and of the "Research Participants' Bill of Rights."

_____ _____
Signature of Participant Date

_____ _____
Name of Participant (printed) Signature of Person Obtaining Consent

Kaiser Permanente Medical Care Program
Research Participants' Bill of Rights

The following rights and privileges are guaranteed to all participants in medical research, investigation, or experimentation conducted within the HMO. If you have questions about these rights, please call the IRB NAME AND PHONE NUMBER.

Persons who participate in medical research are entitled to certain rights which include, but are not necessarily limited to, the right to be:

1. Informed of the nature and purpose of the study, investigation, or experiment in which they are being asked to participate.
2. Given an explanation of the procedures to be followed in the medical study, investigation, or experiment and a description of any drug or device to be used.
3. Informed of any related discomforts and risks that can reasonably be expected from participation in the study.
4. Told of any benefits that can reasonably be expected from study participation.
5. Advised of any appropriate alternative procedures, drugs, or devices that might be advantageous to the study participant and the relative risks and benefits of these alternatives.
6. Informed of the availability of medical treatment after the experiment, should complications arise.
7. Given an opportunity to ask any questions concerning the study, investigation, or experiment, or about the procedures involved.
8. Instructed that consent to participate in the medical study, investigation, or experiment may be with drawn at any time with no effect on the participant's health care benefits or medical care provided by HMO.
9. Given a copy of the written consent to participate in the research study, which has been signed and dated by the participant and investigator.
10. Allowed to decide to consent or not to consent to participate in a medical study, investigation, or experiment without the intervention of any element of force, fraud, deceit, duress, coercion, or undue influence upon the participant's decision.

Appendix 3:
Draft Recruitment Materials—
Recruitment Letter

Draft invitation letter for blood and saliva collection assuming active consent and scheduled appointment (printed on local letterhead and using local envelopes)

Name
Address

Dear_____,

You are invited to participate in a long-term study of the genetic basis of disease and response to medications. You were sent this letter because you receive your medical care at _____ (or belong to_____ health plan) and were identified in our records as having breast cancer. Researchers want to learn more about why some women treated for breast cancer develop adverse outcomes such as heart problems. In the future, it may be possible to predict who would develop these problems and treat them appropriately ahead of time. The project is funded by the National Cancer Institute and involves investigators at multiple institutions.

Participation in this study involves completing a brief questionnaire about your health habits and providing a blood/saliva sample. We will also link your sample to your medical records for our analysis. After we gather the important health information from your records, all elements that can identify you will be destroyed and the de-identified information will be stored indefinitely. These de-identified samples and data may be shared with external investigators after proper approval. Your participation will take approximately _____ minutes and will help. (You will be offered $_____ for your time).

A Research Coordinator/Assistant will contact you within the next two weeks to explain the study in more detail, answer any questions that you may have, and find out if you are interested in scheduling an appointment to participate. If you would like to read more about the project before that, feel free to browse the study web site at www._____. If you want to speak to someone in person or decline participation, please call our toll free number_____.

Thank you for taking the time to learn more about our project and consider participation. Research results are only possible through participation by individuals such as yourself.

Sincerely,

_____ _____

Site Principal Investigator Overall Principal Investigator

Appendix 4:
Guidelines for Budgeting for Saliva/Blood Collection

Blood Collection Protocol for Breast Cancer Cohort
Items to Consider for Budget Estimation
Recruitment/enrollment Only

1. **Administration**

Personnel

Task	Person responsible	Time
IRB approval	Research Coordinator	1 week
Weekly study meetings	All staff	four hours per week
Project oversight	PI	10% time

Consumables

Monthly one-hour teleconferences

2. **Recruitment**

Personnel

Task	Person responsible	Time
Mailings to eligible patients	Secretary	20 per hour
Follow-up phone calls	Research Coordinator	1 hour per subject enrolled

Consumables

Letterhead
Envelopes
Postage
Telephone calls

3. **Enrollment**

Personnel

Task	Person responsible	Time
Informed consent process	Research Coordinator	30 minutes per subject

Consumables

Paper for consent forms in duplicate
Paper for any questionnaires
Labels for consent forms and questionnaires
Computer and printer for managing data and printing labels
Subject incentive
Participant refreshments

Travel

If going to other sites

4. Specimen Processing

Personnel

Task	Person responsible	Time
Blood draw	Phlebotomist	15 minutes per subject
Shipment of Sample/packaging		
Spin blood, extract DNA, aliquot, measure quantity and quality, label samples and enter into tracking system	Lab Tech	Depends on technique
Identify tumor samples for subjects and note in VDW	Programmer	2 hours monthly

- Ship weekly? Labeling/packaging/paperwork/tracking

Consumables

Tubes for blood draws
Tubes and labels for DNA aliquots
Freezer racks
Lab supplies
-80 freezer if not available

5. Data Management

Personnel

Task	Person responsible	Time
Develop subject tracking system for recruitment/ enrollment	Programmer	1 week
Develop or install patient tracking system for samples	Programmer	1 month
Initial Data Pull Note existence of samples in VDW	Programmer Programmer	2 weeks 2 hours monthly

- Development can be conducted centrally, and then distributed

Consumables

Possibly hardware or software

Appendix 5:
List of proposed variables for a ‘database of studies’

Name of study

Abbreviated name

PI

Years of recruitment

Number of subjects

Age and gender distribution of subjects

Type(s) and quantity of sample collected

Informed consent to share data and/or samples for future studies (limitations of informed consent)

Contact person and contact information

Study website link

Ability to re-contact study subjects for additional samples or information

Brief study description (1-3 sentence synopsis)

Estimate number of various cancers, ideally by 10-year age group and gender

Opt in/opt out recruitment

Abstract

PDF of informed consent form

Appendix 6:
Documentation of procedures & policies from existing sites with tumor repositories

KAISER PERMANENTE®

NORTHERN CALIFORNIA KAISER PERMANENTE RESEARCH BIOSPECIMEN COORDINATING CENTER (RBCC)

POLICY GUIDELINES AND PROCEDURES FOR STUDIES REQUESTING USE OF KAISER PERMANENTE BIOSPECIMENS

RBCC Committee Members:
Charles Quesenberry, PhD, Senior Biostatistician, Chair
Balaram Puligandla, MD, Chief of Pathology, KPMC, Oakland
Laurel Habel, PhD, Research Scientist
Stephen Van Den Eeden, PhD, Research Scientist
Judith Morse, Biospecimen Coordinator

Address Correspondence to:
Judith Morse
Kaiser Permanente, Division of Research
3505 Broadway, 8th Floor
Oakland, CA 94611
510.891.3248
Fax: 510.891.3249
Email: judith.c.morse@kp.org

Overview

In January 2000, Northern California Kaiser Permanente Medical Care Program (KPMCP) Chiefs of Pathology and Research Scientists at the Division of Research established a centralized Research Biospecimen Coordinating Center (RBCC). The overarching goal of this Center is to establish uniform policies and procedures to maximize the research potential of the KPMCP Pathology Archive and the Kaiser/Orentreich Serum Repository, while protecting the interests of patients and clinicians.

Specific aims of the RBCC are to:

- *Ensure the careful stewardship and management of KPMCP's biospecimen collections used for research purposes*
- *Maintain a centralized organizational structure and standardized protocols to minimize the burden of research requests on pathology department staff*
- *Establish policies and protocols to support patient rights, progress in medical science, and the research agenda of KPMCP*
- *Guarantee that the costs of research are borne by study budgets and not by pathology or other KPMCP departments*

Policy Guidelines

- All requests for biospecimens must undergo a review process (see procedures).
- Requests for biospecimens for research purposes should be made directly to the RBCC.
- Pathology materials will be retrieved by RBCC staff.
- Prior to the release of biospecimens, study investigators must sign an agreement to follow established policy guidelines and procedures (see draft agreement).
- A collaborating KPMCP pathologist should be identified for research projects, whenever possible.
- The use of a specimen for research purposes must not compromise the medical information contained in the specimen (e.g., diagnostic slide, block) and patients' confidentiality should be protected. Bio-ethics and HIPPA guidelines will be strictly followed on all projects.
- In order to minimize the risk to specimens, the use of the services of the KPMCP Regional Laboratory for sectioning and staining of materials is required, except when special processing of pathology materials is needed.
- In general, requests for transfer of biospecimens from the KPMCP Pathology Archive or the Kaiser/Orentreich Serum Repository to external specimen banks will not be granted.

Procedures For Requesting Biospecimens

1. Complete and submit application to Judith Morse. Applications (for pathology or serum) and a fee structure are available by contacting Ms. Morse by phone (510.891.3248); email to judith.c.morse@kp.org.

   Note: we encourage interested researchers to identify a KP collaborator before seeking funding for studies involving significant numbers of biospecimens. This will also help to prevent overlap with studies in progress or in the planning stage.

2. Applications will be reviewed monthly by committee members of the RBCC. Whenever possible, the applicant should make themselves available (by phone) to address concerns and answer questions. A schedule and agenda for upcoming meetings are available by contacting Ms. Morse.

3. Following approval of the application, an agreement (addressing scientific and financial issues) between the RBCC and the research institute will be developed and signed by both parties.

4. RBCC personnel will make arrangements with pathology departments for the retrieval of the needed materials.

Preparation for retrieval/processing of materials:

- An informational packet, prepared with the help of the study Principal Investigator, will be sent to each Chief of Pathology at the Department where materials of interest are located. The informational packet will include a letter with a brief description of the protocol, the study abstract, and a listing of study subjects and pathology accession numbers. The chief of pathology has the right to refuse use of materials for research purposes.

- Protocols must be in place to ensure that materials can be returned to the originating pathology departments as soon as possible and within 48 hours, if requested for clinical or legal purposes.

- Protocols for sectioning and staining slides, and shipping materials must be provided. Protocols should have the diagnostic slides reviewed and blocks sectioned by KP pathology personnel, except when special processing of pathology materials is needed.

- Protocols must be in place to ensure that biospecimens are not exhausted in the course of the research study. (See Below.)

  Note: blocks with only small amounts of material will not be available for research purposes.

PROCEDURES* FOR SPECIMEN SAFETY AND QUALITY CONTROL

1. Safeguards to address medical-legal concerns

- All precautions should be taken to prevent exhausting tissue blocks.
- Blocks will be returned to pathology departments within 8 weeks of submission, unless otherwise arranged.
- Diagnostic slides will be returned to the submitting pathology department within 48 hours of a request.

2. Quality control of storage and sectioning of tissue blocks

The following factors will be considered:

- Appropriate processing of blocks and storage of cut sections to minimize antigen deterioration.
- Appropriate cutting schema to accommodate laboratory assays that includes quality assurance that representative sections are obtained for each assay.

3. Quality assurance of stored/sectioned material

Protocols should be specified for the following, when appropriate:

- Selection of representative blocks
- Marking of 'tumor rich' vs. 'tumor poor' on the H & E slides for DNA studies, and on the blocks for tissue microarrays, etc.

***Note: We strongly encourage you to consider adopting procedures outlined in:**

Dressler et al. Policy guidelines for the utilization of formalin-fixed, paraffin-embedded tissue sections: the UNC SPORE experience. Breast Cancer Research and Treatment 1999;58:31-39.

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Application to Obtain Pathology Materials from Northern California Kaiser Permanente facilities for Research

Project Title

Funding Source and Status

PI

Printed Name	Signature	Date
( )	( )	
Phone	Fax	Email

PI affiliation and title:

Please address each of the following:

1. Kaiser Permanente collaborators (names and affiliation)
2. Non-Kaiser Permanente collaborators (names and affiliation)
3. Status of funding (specify agency)
4. Anticipated start date (and study duration)
5. Study overview (proposal abstract or summary of specific aims, significance, methods)
6. Statistical power/number of subjects (Kaiser and non-Kaiser, separately)
7. Detailed description of the material(s) requested (e.g., diagnostic years of interest, type of materials needed (pathology reports, slides, blocks)). If blocks are to be sectioned, specify number and thickness of sections/block needed.
8. Detailed description of protocols that will use pathology materials (e.g. specific tumor marker assays)
9. Procedures to ensure specimens are not exhausted
10. Procedures to ensure specimens are safely returned to Kaiser Permanente
11. Copy of patient consent to release materials (when appropriate)
12. Procedures to ensure patient confidentiality
13. Status of local IRB approval
14. Status of formal peer review (specify review group)

Please note:
The Kaiser Permanente Biospecimen Coordinating Center policy requires the return of all data obtained from the specimens utilized, including, but not limited to standardized re-review results, and assay results.

Please send completed applications to:
Northern California Kaiser Permanente
Research Biospecimen Coordinating Center
3505 Broadway Oakland CA, 94611-5714
Attention: Judith Morse
Email: judith.c.morse@kp.org

Note: Applications are reviewed monthly

KAISER PERMANENTE®

Kaiser Permanente Southern California Research Biospecimen Coordinating Committee (RBCC)

Policy Guidelines and Procedures For Studies Requesting Use of Biospecimens

RBCC Steering Committee Members:
Gary Gochman, MD, Chief of Anatomic Pathology
Reina Haque, PhD, Senior Scientist, Research & Evaluation
Virginia P. Quinn, PhD, Senior Scientist, Research & Evaluation

RBCC Coordinator
Michelle McGuire, MA

Consultants/Sponsor
Michael Kanter, MD, Associate Medical Director, SCPMG
Paul Dieter, MD, JD, SCPMG Legal

Contact information:

- Michelle McGuire, MA
  Kaiser Permanente, Department of Research & Evaluation
  100 S. Los Robles, 2nd Floor, Pasadena, CA 91101
  626.564.7104, Fax: 626.564.3430, email: Michelle.M.McGuire@kp.org
- Reina Haque, PhD, email: Reina.Haque@kp.org
  Admin Assistant: Lisa Eklund, 626.564.3466

Kaiser Permanente Southern California RBCC

Table of Contents

KPSC Regional Biospecimen Coordinating Committee
Standard Operating Procedures

Overview

In May 2005, Research Scientists in the Research & Evaluation Department and the Southern California Permanente Medical Group Chiefs of Pathology established a centralized Research Biospecimen Coordinating Committee (RBCC) to ensure the careful stewardship and management of KPSC's biospecimen resources. The overarching goal of the RBCC is to establish uniform policies and procedures to maximize the internal and research potential of the SCPMG Pathology Archive while protecting the interests of patients, clinicians and the KPSC organization.

All use of KPSC specimens (archived tissue, fresh or frozen tissue) require prior RBCC review. The specimens/data can only be used for the purposes described in the application. Future or additional uses of the specimens/data must be submitted to the RBCC for review and approval. If specimens or data are to leave KPSC, applications submitted to the RBCC must be accompanied by an approved KPSC IRB protocol and appropriate data use or material transfer agreements.

Use of KPSC biospecimens for internal use (i.e., quality control, patient management project, tumor board presentation, grant proposal work). KPSC specimens and any data or statistical results based on these specimens/data can be reported only in internal KPSC reports, and cannot be included in a scientific manuscript to be published outside of the KPSC organization, including the Permanente Journal. In addition, the specimens/data may not be shared with any person or organization outside KPSC.

Requests requiring the provision of identifying information such as name or medical record number confer the responsibility of ensuring compliance with the privacy requirements.

Use of biospecimens for external use (research, publication, collaboration with university faculty or biotech company, resident studies if for publication). In addition to a complete RBCC application and KPSC IRB approval, requests for external use must also include a study budget and appropriate legally executed contracts and agreements (See page 8 for details).

All projects for external use require a KPSC PI to assume responsibility for the scientific integrity of the project, HIPAA Compliance and financial oversight (See page 7 for details).

We require interested external researchers (including residents) to identify a KPSC Site PI to serve as a collaborator prior to seeking funding for studies involving KPSC biospecimens.

The costs per accession for external (non-SCPMG studies) are listed on page 11.

The RBCC Committee encourages investigators to contact the RBCC project coordinator at the earliest possible stage to ensure that the cost of specimen retrieval, staff and overhead are adequately covered by the study budget.

A minimum of **4 weeks** will be required for processing applications after submission of all required documents to the RBCC.

Flowchart for requesting KPSC specimens for research

Internal Use
(Specimens/data will remain within KPSC)

Examples Include:

- Quality Control
- Patient Management Project
- Tumor Board Presentation
- Grant Preparation

Submit approved RAPTOR form if applicable (see pg. 7)

▼

Complete RBCC Application
Submit to RBCC Coordinator (see pg. 13)

External Use
(Specimens/data will be released or published outside KPSC)

Examples Include:

- Publication /Presentation
- Industry Collaboration
- Academic Collaboration
- Resident Projects

▼

Step 1 for RBCC Approval
Submit RBCC Application with KPSC IRB Protocol to RBCC Coordinator (see pg. 13)

Step 2 to Receive Specimens
Submit:

- Appropriate contracts/ agreements (see pg. 8)
- IRB approval letter or exemption letter

The mission of the RBCC is to:

- Ensure the careful stewardship and management of KPSC's biospecimen collections used for internal and research purposes.
- Create and maintain a centralized system to track the use and location of KPSC members' biospecimens.
- Maintain a centralized organizational structure and standardized protocols to minimize the burden on pathology department staff.
- Establish guidelines to support patient rights, progress in medical science and the research agenda of SCPMG.
- Guarantee that the costs of research are covered by study budgets and not by pathology or other departments.
- Enhance the research capacity of KPSC investigators by ensuring SCPMG investigators receive credit for their collaborative work with external groups such as university faculty or biotech companies.

General Guidelines

All requests for pathology specimens must be submitted on the KPSC Application to Obtain Pathology Materials Form (see page 13) and undergo a review process (see review criteria on page 5). KPSC pathology specimens may only be used for the purposes described in the approved application. **Using KPSC pathology specimens in a manner for which they have not been approved can result in IRB and HIPAA violations that can ultimately result in state or federal sanctions against KPSC.** For any change in the proposed use(s) of the requested KPSC pathology specimens, contact the IRB office at 626.405.5972 or tie line 8.335.5972, and notify RBCC staff at 626.564.3466 or tie line 8.338.3466.

1. Biospecimens for Research Use

a. All requests for KPSC pathology specimens must be made directly to the RBCC for review by steering committee members.

b. If use of biospecimen data is for external use (e.g., research, publication, collaboration with university faculty or biotech company), an application, KPSC IRB approval, study budget, and appropriate legally executed contracts must be submitted to the RBCC Coordinator prior to retrieval/use of biospecimens.

c. Pathology materials may be retrieved by RBCC staff to be assembled for shipment to study site. Alternatively, local medical center staff may be used with department chief's approval. Funds are required to support KPSC staff time. Non-KPSC employees are prohibited from obtaining, retrieving or re-filing or returning any data or biospecimens from any KPSC medical or storage facility.

2. KPSC Principal Investigator/SCPMG pathologist

1. All projects for external use require a KPSC PI to assume responsibility for the scientific integrity of the project, HIPAA Compliance and financial oversight (See page 7 for details).
2. A collaborating SCPMG pathologist should be identified for projects using biospecimens.

3. Study Protocols

a. Protocols must be in place to ensure that biospecimens are not exhausted in the course of the research study. (Note, paraffin blocks with only small amounts of material will not be available for research purposes.) In order to minimize the risk to specimens, applicants are required to provide a detailed description of study protocols that describe use of pathology materials as well as procedures to ensure the preservation and integrity of specimens.

b. The use of a specimen for research purposes must not compromise the medical information contained in the specimen (e.g., diagnostic slide, block) and patients' confidentiality should be protected. The KPSC Principles of Responsibility and HIPAA guidelines must be strictly followed on all projects.

c. Protocols must be in place to ensure that materials can be returned to the originating pathology departments as soon as possible and within 48 hours, if requested for clinical purposes.

d. Protocols for sectioning and staining slides and shipping materials must be included in the application to the RBCC.

e. Under no circumstances will data be released to KPSC physicians or employees for personal use.

4. Statement by Requestor

1. KPSC PI must sign a statement describing the use and disclosure of data as part of the RBCC Application to Obtain Pathology Materials (see page 15).

RBCC Review Criteria

Requests for biospecimens will undergo review by the RBCC Steering Committee.

Requests for biospecimens will be reviewed using the following criteria:

1. Scientific merit.
2. Persons/entities who will have access to the data (e.g., programmers, outside collaborators, etc).
3. Plan for protecting confidentiality.
4. Organizational appropriateness and whether the project aligns with the KPSC mission.
5. Overlap with any other internal research studies & interests.
6. Data destruction plan delineating when and how the requestor plans to destroy data used in any analysis.
7. Detailed descriptions of study protocols as well as procedures to ensure the preservation and integrity of specimens.

The RBCC reserves the right to deny a data request.

Data Sharing & Collaborations with External Organizations

Review by the KPSC Institutional Review Board (IRB) is required for all external use projects including other KP regions or to generate data for publication. Requests from KPSC physicians or employees for information for publication, research, and collaborations with outside parties will not be fulfilled without appropriate approvals from the KPSC IRB and the KPSC organization (i.e., subcontracts, Data Use and Confidentiality Agreements). For activities preparatory to research, such as grant proposals, an approved KPSC RAPTOR form must be submitted with the request to the RBCC.

Procedures for Specimen Safety and Quality Control*

Safeguards to address medical-legal concerns

1. All precautions should be taken to prevent exhausting tissue blocks.
2. Blocks must be returned to the RBCC within 8 weeks, unless otherwise arranged.
3. Diagnostic slides must be returned to the submitting pathology department within 48 hours of a request.
4. Either blocks or representative slides for each specimen will be provided. Requests for both blocks and slides will not be granted.
5. Additional fees will be charged for specimens that are destroyed or not returned.

Quality control—storage and sectioning of tissue blocks

The following factors will be considered:

1. Appropriate processing of blocks and storage of cut sections to minimize antigen deterioration.

Quality assurance of stored/sectioned material

Protocols should be specified for the following, when appropriate:

1. Selection of representative blocks.
2. Marking of 'tumor rich' vs. 'tumor poor' on the H & E slides for DNA studies and on the blocks for tissue microarrays, etc.

***Note: We strongly encourage you to consider adopting procedures outlined in:**

Dressler et al. Policy guidelines for the utilization of formalin-fixed, paraffin-embedded tissue sections: the UNC SPORE experience. Breast Cancer Research and Treatment 1999;58:31-39.

Preparation for Retrieval/Processing of Materials

When the RBCC approves the request, an information packet prepared by RBCC staff with the help of the study Principal Investigator will be sent to each Chief of Pathology at the departments where materials of interest are located. The information packet will include a letter with a brief description of the protocol, the study abstract and a listing of study subjects and pathology accession numbers.

Expectations of KPSC Principle Investigators Including Physicians, Scientists and Staff Collaborating with External Entities

- All projects for external use (e.g., research, publication, collaboration with university faculty or biotech firms) require a KPSC PI.
- KPSC PI will assume responsibility for:
  - Completing the IRB application/request for expedited review.
  - HIPAA Compliance.
  - Financial oversight for the project.
  - Initiating subcontracts (i.e., material transfer and/or data use agreements) with the external organization.
- There is an explicit expectation that the KPSC site PI will participate in the design, implementation of the research protocol, analysis and manuscript preparation for the study.
- It is expected that the study budget will provide for 5-10% FTE for the KPSC site PI, as well as funds adequate to cover staff time for specimen retrieval.

  Link to useful information and forms:
  http://researchweb.lsrs.ca.kp.org/topbar/sitemap.htm

  Webpage includes:
  - Raptor Form (for preparatory research activities, e.g. pilot studies where you will not access PHI)
  - IRB application
  - Research & Evaluation
  - Research Finance (contact Sharon Figgins, Director of Research Finance, 626.564.3135, tieline 8.338.3135 or at Sharon.M.Figgins@kp.org
    - Contracts & Grants (e.g., DUA's, confidentiality agreements, etc.)

Checklist for Biospecimen Requests

Internal Studies (SCPMG Physicians /Investigators using KPSC specimens)

- Complete and submit KPSC RBCC Application Sections 1-3 (see page 13)
  - ( ) Investigators' signatures and complete contact information.
  - ( ) Detailed protocols (i.e., use of biospecimens, safeguarding of biospecimens, data destruction plan, confidentiality protection).
  - ( ) Include approved KPSC IRB/RAPTOR form if request is for preliminary data for a grant proposal.

External Studies (specimens and/or data will be released or published outside KPSC)

- Complete and submit KPSC RBCC Application (see page 13)
  - ( ) Investigators' signatures and complete contact information.
  - ( ) Submit KPSC IRB application with detailed protocols (i.e., use of biospecimens, safeguarding of biospecimens, data destruction plan, confidentiality protection).
- Submit KPSC IRB approval/exemption letter to the RBCC coordinator.
- Submit fully executed subcontracts/agreements to the RBCC coordinator. A Material Tranfer Agreement (MTA) is required when requesting biospecimens for external use, MTA's also apply to any data, information or any product derived from the KPSC biospecimens. A Data Use Agreement (DUA) is required when KPSC data is requested for external use. Contact Research Finance for further information about which agreements are required. (http://researchweb.lsrs.ca.kp.org).
- Submit study cost center number if the cost of specimen retrieval and refilling is not covered by local medical centers (see page 11 for the cost of services).

Frequently Asked Questions*

1. **Do I need to complete the application if I am using only my medical center's specimens/slides?**

   Yes. At the March 2007 Chief's group meeting, there was an agreement to centrally track all specimens used for internal and external purposes.

2. **Do surgery patients sign any type of consent for or release of their tissue?**

   The consent form signed by patients, Consent to Operation, Administration of Anesthetics and the Render of Other Medical Services, contains the following statement: "I hereby authorize the hospital and medical group to dispose of any severed tissue or member in accordance with accustomed hospital practice."

3. **Who owns the specimens?**

   California law on ownership of specimens was extensively explained by the Supreme Court of California in Moore v. Regents of University of California (51 Cal.3d 120) Jul 9, 1990.

   The KPSC Medical Care Program owns the specimens although the patient has the right to access them. In the ordinary medical activities of the KPSC Medical Care Program regarding the financial value of tissue, we are at relatively little risk. Routinely removed tissue has no significant value. However, tissue has a significant value only if it has been passed through some research project that demon strates a unique attribute that makes it particularly valuable.

   It is exceedingly rare that human tissue has a unique attribute that makes it particularly valuable. To avoid the risk that might arise if a research project demonstrates that the specimen of a patient has a unique attribute that makes it particularly valuable, our IRB and other research compliance activities extensively address misuse of research to gain secret profits as occurred in the Moore case.

4. **Is it true that cytology specimens cannot be removed from the medical facility premises and are available only for on site review?**

   It is the practice of the KPSC Medical Care Program to retain cytology specimens on site. There are several reasons for storing biospecimens at KPSC medical facilities:
   a) Statutes exist that require that tissue be retained for a particular length of time.
   b) Tissue specimens may be valuable for the continued care of patients. To assure their availability, these tissues are kept on site rather than stored elsewhere.
   c) If litigation is in process or threatened, tissue samples that are unique and cannot be reproduced are retained rather than produced on subpoena or other legal process.

5. **What if I need to outsource pathology review (e.g., to a vendor or academic collaborator)?**

   a) A secure storage system which allows for timely retrieval of specimens when requested is required.
   b) Your IRB protocol must outline the steps that will be taken to maintain secure storage and ensure that patient identification information linked with specimens are kept separately.
   c) If specimens are to be sent outside the KPSC organization, you will need: 1. Business Associate Agreement, or 2. Data Use Agreement (contact Research Finance for assistance).

*Responses to questions 2-5 provided by: Dr. Paul Deiter, M.D., LL.B. Counsel, Southern California Permanente Medical Group. Personal communication, May, 2007.

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KPSC Regional Biospecimen Coordinating Committee
Application to Obtain Pathology Materials

Is the project:

Internal (within KPSC region only)

External (non KPSC, including other KP regions)

SECTION 1

Project Title:

KPSC IRB Approval #:

Funding Source and Status:

Submit study cost center number if the cost of specimen retrieval and refilling is not covered by local medical centers (see pg 11 for the cost of services)

Number of accessions requested:

KPSC Principal Investigator:

Printed Name	Signature	Date

Phone	Fax	Email

Principal Investigator affiliation and title:

Non-KPSC Collaborators:

Name	Affiliation	Email

(Insert names of additional collaborators & contact information here)

SECTION 2

Timeline, Data Retention/Destruction:

When do you need the tissue?
Anticipated timeline

- Project start date
- Number of months to complete the project
- Date when access to specimens will no longer be required
- Date when specimens will be returned
- Date when data (electronic or hardcopy) will be destroyed

SECTION 3

1. Data Linkages: Please complete if results of biospecimen assays will be linked to other KPSC databases (e.g., pharmacy, outpatient, inpatient, etc.).

   Databases to which linkage is planned:

   _____

   _____

   _____

   _____

   _____

2. Detailed description of the material(s) requested (e.g., diagnostic years of interest, type of materials needed (pathology reports, slides, blocks)
3. Detailed description of protocols that will use pathology materials (e.g. specific tumor marker assays)
4. Procedures to ensure specimens are not exhausted

APPEND LIST OF MRNS AND ACCESSION NUMBERS AND LOCATIONS OF BIOSPECIMENS SECTION 4 (FOR EXTERNAL PROJECTS)

Provide the following information on a separate sheet:

1. Status of funding (specify agency):
2. Statistical power/ number of subjects (Kaiser and non-Kaiser, separately)
3. Procedures to ensure specimens are safely returned to Kaiser Permanente

Statement by Requestor

1. Requestor agrees that she/he will not pass PHI, or derivative files (i.e., de-identified data sets) on to any other party without the express written consent of the KPSC IRB and approval by the RBCC Committee.
2. Requestor will bear all risks resulting from its publication or presentation.
3. Requestor agrees to destroy all files, documents or other records containing KPSC data in their custody at the earliest opportunity consistent with the conduct of the proposed use unless there is a health or research justification for retention or retention is required by law. Notwithstanding the foregoing, requestor agrees to destroy all files, documents or other records containing KPSC data in their custody no later than necessary to complete the work, but no longer than the end of the study; unless the RBCC Committee, at its sole discretion, extends the deadline for destruction after consideration. The Requestor is responsible for submitting a request for such an extension by written notice to the RBCC Coordinator.

Destruction means physical destruction of files or deletion of electronic data related to the specimens, documents or other records. De-Identification shall not be considered destruction.

4. All reasonable efforts will be made to limit the use or disclosure of PHI to only that which is necessary to accomplish the intended purpose.
5. The Researcher understands that some data may contain confidential information about individual patients and other identifiers such as names of physicians, hospitals and laboratories or may otherwise be in a form (pathology report) where individual patients may be identifiable. The Requestor agrees to ensure security and protection of identifiable record level data as follows:

   - Biospecimens (blocks, slides) and related paper copies of records will be kept in access-protected premises.
   - Access to the computers and records stored in them will be restricted through use of passwords and other appropriate access control procedures.
   - If photocopied, identifiers will be obliterated completely.
   - Electronic files containing PHI (e.g. magnetic and optic disks, CDs and cartridges) will be destroyed at the end of the study.
   - All study related electronic files will be transferred through secure electronic file transfer methods.

6. If the Requestor is working with external collaborators (e.g., universities or other institutions), the Requestor will be responsible for having each of these persons sign Confidentiality Agreements. In addition, the Requestor is responsible for establishing a Data Use Agreement/Material Transfer Agreement with each external institution. The Requestor is responsible for sending these documents to the KPSC RBCC prior to committee review. No other person shall have access to the records in a form where individuals may be identifiable.

Contact Research Finance to initiate these agreements (Sharon Figgins, 626.564.3135 or tie 8.338.3135, Sharon.M.Figgins@kp.org).

7. Append IRB application. A copy of the IRB approval letter must be provided to the RBCC Coordinator prior to the retrieval and release of any specimens.

8. If KPSC specimens or data will be released or published outside KPSC, append legal subcontracts and study budget or cost center to be charged (see #6 above).

The Principal Investigator certifies that the information reported in this form and the Research Project Proposal is accurate and agree to comply with the terms and conditions contained in this form.

KPSC Principal Investigator:

Signature

Printed Name

Date

Principal Investigator's affiliation and title

Cost Center to be charged for retrieval of specimens

Please send completed applications to:

Kaiser Permanente Southern California
Department of Research & Evaluation
100 S. Los Robles, 2nd Floor, Pasadena, CA 91101

Attention:

Michelle McGuire, MA, RBCC Coordinator
& Reina Haque, PhD

Email: michelle.m.mcguire@kp.org
Email: reina.haque@kp.org
Fax: 626.564.3409

Appendix 7:
Best Practices Guidelines

Biorepositories Best Practices Resource List

1) International Society for Biological and Environmental Repositories http://www.isber.org/
   a. 2008 Best Practices for Repositories http://www.isber.org/Pubs/BestPractices2008.pdf

2) National Cancer Institute Office of Biorepositories and Biospecimen Research
   http://biospecimens.cancer.gov/default.asp
   a. Best Practices for Biospecimen Resources
      http://biospecimens.cancer.gov/global/pdfs/NCI_Best_Practices_060507.pdf
   b. How to Establish and Manage a Tissue Bank or Other Specimen Resource
      http://www.cancerdiagnosis.nci.nih.gov/specimens/establish.htm
   c. NCI Specimen Resource Locator http://pluto3.nci.nih.gov/tissue/default.htm

3) Australasian Biospecimen Network http://www.abrn.net/
   a. Australasian Biospecimen Network Biorepository Protocols—Revision 4
      http://www.abrn.net/pdf/ABN_SOPs_Review_Mar07_final.pdf

4) RAND http://biospecimens.rand.org/
   a. Case Studies of Existing Human Tissue Repositories: “Best Practices” for a Biospecimen Resource for the Genomic and Proteomic Era
      http://www.rand.org/pubs/monographs/MG120/index.html

5) Public Population Project in Genomics (P3G) Observatory
   a. http://www.p3gobservatory.org

6) Organization for Economic Cooperation and Development
   a. Guidelines for Human Biobanks and Genetic Research Databases
      www.oecd.org/sti/biotechnology/hbgrd
   b. Creation and Governance of Human Genetic Research Databases
      http://www.oecd.org/document/50/0,3343,en_2649_34537_37646258_1_1_1_1,00.html