

Kaiser Permanente Northwest (KPNW) Population, Demographics, and Phenotypes

Table 1 shows the demographic characteristics of KPNW members. KPNW's members are demographically representative of the coverage area and represent about 20% of the area's population. Medicare members represent about 12% of KPNW's total membership, and 2% are below 200% of the federal poverty level.

Characteristics of Study Cohorts

Our biorepository includes specimens from 68,645 subjects recruited through three studies that we will refer to as the CVL, the HEIRS, and the NW BIOBANK cohorts. We describe the demographic and phenotypic characteristics, the recruitment method, and the consent process for each cohort. The CVL and HEIRS cohorts are legacy specimens from previously conducted research studies. Only the NW BIOBANK study is currently prospectively recruiting subjects.

NW BIOBANK Cohort

The NW BIOBANK has been developed with resources provided by KPCHR and OCTRI. In initial phases we have designed and tested key features of this repository, including its governance structure; methods of sample storage, handling, and retrieval; the consent process; and data security. By recruiting KPNW members over multiple years, we plan to ultimately invite all 330,000 adult members to contribute a blood specimen, and to recruit 100,000 members.

One logistical problem for many repositories is that widespread geographical distribution of participants runs counter to the efficiencies gained by centralizing study activities. KPNW, however, has an integrated sample acquisition and analysis infrastructure that is unusual among U.S. healthcare providers. Members obtain healthcare at any of 26 facilities spread over a 100-mile region from Salem, OR to Longview, WA. Although blood draws occur at all of these facilities, most blood samples are processed at a regional laboratory. A dedicated courier service ships samples to the central facility as often as every two hours. Vacutainer tubes are labeled with unique barcode numbers, which tracks the blood samples and are linked to the patient's health record number. After clinical diagnostic testing the blood samples are normally discarded. For the NW BIOBANK, KPCHR intercepts blood samples before they are discarded and uses these residual samples as the basis for the biorepository.

Each year, KPNW collects over 300,000 tubes of blood as part of routine medical care, providing significant potential to rapidly obtain specimens from numerous patients. To enable the broadest possible collaborative opportunities for the NW BIOBANK, when we collect samples we request consent specifically to use them for genetic research, and to share them with researchers, including through dbGaP. Failing to obtain consent for these explicit purposes could limit future use of the materials.

We have completed two waves of pilot recruitment. In October 2009, we mailed 2,000 invitations to patients eligible for a study on thiazide use in hypertension cases. The response rate was 34%; 82% of respondents agreed to contribute a specimen. In six months we have obtained residual blood specimens from 38% of consented subjects. In April 2010, we mailed a second wave of invitations to all current KPNW members with a history of breast cancer diagnosis (4921 cases) and to 2000 matched controls.

Since 2010 we completed several recruitment approaches. To date, we have received consent from 25,982 subjects for the NW BIOBANK and we were able to collect over 15,000 specimen.

Table 1. Characteristics of Current Member Populations at KPNW		
Total Enrollment x 1000		490
Male, %		48
Race, %	White	81
	African American	3
	Asian	5
	American Indian	0
	Hispanic	8
	Hawaiian/Pacific	1
Age, years, %	≤ 24	29
	25-44	26
	45-64	29
	65-74	10
Retention, %	1-year	94
	3-year	71
	5-year	57

CVL Cohort

During 1989-90, KPCHR collected cervicovaginal lavage (CVL) specimens from 23,702 women coming to KPNW clinics for routine pelvic exams and Papanicolaou (Pap) smears. The women in this sample were unselected KPNW members coming to a variety of providers for routine visits, which included a pelvic examination and Pap smear screening. This study was reviewed by the KPNW Institutional Review Board (IRB), who judged that the CVL procedure was of minimal risk and waived the need for signed informed consent. Anyone could refuse the CVL procedure, and 1071 women declined to participate.

Frozen samples were sent to SeraCare BioServices, in Gaithersburg, MD which is under contract with the National Cancer Institute (NCI). In July, 2010, the specimens were transported in freezers back to KPNW's facility. The aim of the study was to investigate determinants of cervical cancer, particularly the role of the human papillomavirus (HPV). This was among the first epidemiologic studies to establish that HPV infection is implicated in the majority of cervical intraepithelial neoplasias. Subsequent studies have generated over 30 publications. All studies were approved by the KPNW IRB, many involved direct patient contact and specific informed consent. Specimens for 19,474 women are still available.

Table 2. Demographic Characteristics of Study Populations					
		CVL	HEIRS		NW Biobank
			NW	HI ⁴	
Total Enrollment		22,356	13,570	6,737	25,982
Female, %		100	63	60	59
Race, %	White	91%	93%	50%	94%
	African American	4%	2%	0.8%	1%
	Asian	2%	1%	38%	1%
	Am Indian	0%	0%	0.3%	0%
	Hispanic	2%	2%	0.6%	2%
Mean Age, yrs, (range)		37 (16-94) ¹	57 (25-100) ²	57 (25-94) ²	71 (4-106)
EMR, %	At least 1 year	65%	98%	81%	100%
	At least 3 years	55%	92%	75%	98%
	At least 5 years	48%	87%	70%	94%
	10 or more years	37%	70%	N/A ³	83%

¹Age distribution at recruitment about 20 years ago in 1989-1990.
²Age distribution at recruitment about 10 years ago in 2001-2002.
³Not applicable because the KPH EMR was initiated in 2005.
⁴Data as of 2010

The HEIRS Study was designed to examine, in a sample of 100,000 adults, the prevalence, expression, determinants, and potential clinical, personal, and societal impact of hereditary hemochromatosis (iron overload). The HEIRS study target population was primary-care patients. Other volunteers (members accompanying friends or family members to a clinic visit) were not excluded. Enrollment criteria were: at least 25 years of age; able to give informed consent; and current KP membership at KPNW or Kaiser Permanente Hawaii (HI). Over 160,000 KPNW members were contacted by mail.

Participants gave written informed consent, but consent only included future studies on iron status related phenotypes. Participants were enrolled in 2001-2002.

A casual (fasting or non-fasting) blood sample was drawn from each participant to obtain serum for transferrin saturation (TS) and serum ferritin (SF) levels and DNA for testing for *HFE* C282Y and H63D variants. Study criteria for assigning a positive result were: TS>50% and SF>300 µg/L for men and TS>45% and SF>200 µg/L for women. A follow-up clinical evaluation was offered to all *HFE* C282Y homozygotes and to participants with elevated SF and TS levels. Blood specimens from these subjects are stored at NIH (<https://biolincc.nhlbi.nih.gov/studies/heirs/>). Currently, there are about 78,000 buffy coat, 9,000 DNA, 8,000 lymphocytes, 169,000 serum, and 4,500 plasma samples from HEIRS study subjects. Although any qualified researcher can request access to the specimens and linked data, the consent form specifically limits the use of specimens to “studies related to iron overload and Hereditary Hemochromatosis”.

Table 3. HEIRS Re-Consent	Current Members	Former Members
	N	N
Mailing (Total N 11859)	8238	3621
Bad Address	21 (0.3%)	499 (14%)
Refused	73 (0.9%)	30 (0.8%)
Deceased	22 (0.3%)	37 (1%)
Total Consented	5078 (62%)	857 (24%)

In 2011 the NWBB conducted a recruitment mailing approach to the former HEIRS population to consent participants to broader research. For the re-consent process, we excluded participants who were known to be deceased (13%). We used the last known address from the KPNW records. About 69% of the remaining HEIRS participants are still current KPNW members, Table 3. KPNW can request specimens for research if the subjects re-consent to broader future uses of their specimens needs to go through an application process to request specimens from BIOLINCC.

Demographic & Phenotypic Characteristics of Study Cohorts

There are 68,645 subjects across all three cohorts, Table 2. Most participants are female (74%) because of the recruitment criteria (for CVL and NW BIOBANK) or because women were more likely to agree to participate (for HEIRS). The majority of subjects are White (81%). Most participants have a substantial amount of medical record data, with over 75% having ≥ 5 years of accumulated medical history. The study cohorts include patients with conditions of significant interest to NIH (Table 4), based on priorities in the Healthy People 2010 using ICD9 codes to identify diagnoses.

TABLE 4. PHENOTYPIC CHARACTERISTICS OF STUDY POPULATIONS			
	CVL N = 22356	HEIRS(NW) N= 13570	NWBB N = 25982
Controls ²	9346	919	397
Conditions ¹ :			
Hypertension	6108	8102	18636
COPD	5237	6038	11760
Asthma	3006	3313	5934
Coronary Heart Disease	1346	3312	7870
Stroke	1319	2559	5535
Sleep Apnea	942	1884	3667
Myocardial Infarction	468	1101	2863
Cancer (other)	2433	3607	9441
Breast Cancer	937	655	2826
Prostate Cancer	0	566	1938
Colorectal Cancer	182	287	898
Lung Cancer	182	289	544
Malignant Melanoma	225	310	1157
Obesity	4765	5018	10990
Diabetes	1971	3397	9027
ESRD	52	108	341
Depression	2072	2153	4594
ADHD	164	247	402
Parkinson Disease	123	256	446
Schizophrenia	70	52	80
Alzheimer Disease	191	260	271
Glaucoma	218	359	846
Diabetic Retinopathy	297	649	1631

¹Conditions from the Healthy People 2010 priority areas.

²Controls are defined as individuals who did not have any of 35 conditions in the Healthy People 2010 priority areas.

We also estimated the number of patients who have used common treatments to assess our ability to conduct pharmacogenomic studies (Table 5).

TABLE 5. Treatments used by Study Participants			
	CVL	HEIRS(NW)	NWBB
Anti-Hypertensive: Thiazides	4559	4960	11758
ACE Inhibitors	4910	6970	17465
Beta Blockers	6170	8278	18080
Anti-Hyperlipidemic: Statins	3661	6130	16073
Anti-Platelet: Clopidogrel	414	1109	3426
Anti-Asthmatic: Anti-cholinergics	875	1375	2836
Beta Andrenergics	7185	6453	11960
Steroid Inhalants	3166	3457	6379
Anti-Neoplastic: Anthracyclines	350	203	865
Aromatase Inhibitors	281	191	1046
Anti-Diabetic: Sulfonylureas	1034	1866	4739
Biguanidines	1206	2060	6126
Anti-Depressant: SSRIs	6558	5718	9919

Medispan Generic Product Identifier (GPI) codes were used to identify site specific drug identifiers at KPNW and KPH.