PCGC CHD GENES STUDY MEMORANDUM

TO: NHLBI
From: NERI
Date: August 19, 2014
RE: Demographic and Clinical Summary Data

ENROLLMENT

The study goal is to enroll 10,000 probands by the end of the grant period on 7/31/2015. Enrollment started in October 2010 with a single-site pilot study. Full study enrollment started in November 2010. As of July 27, 2014, 8602 subjects (probands) have been enrolled across 10 centers. Data in **Figure 1** demonstrate that established enrollment targets are being met.

As of July 27, 2014, 23% of enrollments are proband-only, 25% are proband and one parent, and 52% are proband-parent trios. Per protocol, it is expected that all probands will have all parents enrolled.

As of July 27, 2014, 11,350 relatives have been enrolled. Any first-degree relative, as well as affected three-generation relatives, are eligible to enroll. Nearly all (98%) of enrolled relatives are parents.

PROBAND CHARACTERISTICS

As shown in **Table 1**, the proband sample has a mean age of 10.4±12.6 years and a median (inter quartiles) age of 5.5 (0.5, 16.6) with 32% infants. Most patients in the sample are white (78%), and 8% are black. Thirty-two percent have abnormal extracardiac findings. Only a small number of enrolled probands had genetic test results already available. Testing included karyotype (21% abnormal), microarray (30% abnormal), or FISH (19% abnormal).

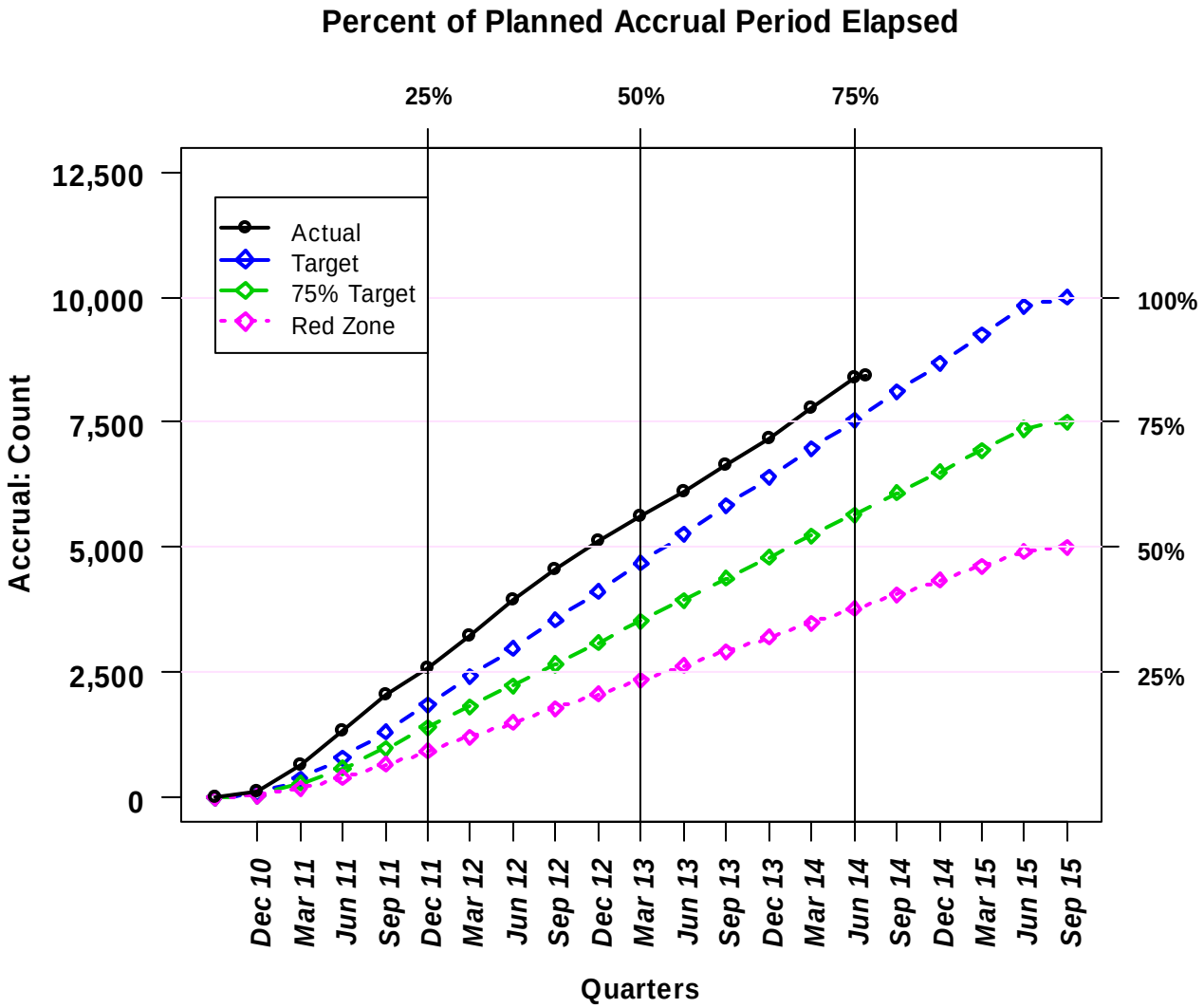
Cardiac diagnosis is collected for CHD GENES using a Fyler coding system. The most common defect in probands is isolated ventricular septal defect (VSD, 28%), followed by atrial septal defect-secundum (ASD, 23%), and tetralogy of Fallot (15%). Eight percent have heterotaxy/related findings. Based on the screening form, 45% of the probands have a conotruncal defect and 20% have a left-sided obstructive lesion.

The distribution of proband anatomic diagnosis by age group is shown in **Table 2.**

CORE LAB SAMPLES

As of July 27, 2014, 8,190 proband specimens have been received at the biorepository, Coriell. Out of these, 940 proband specimens were sent for genotyping, and 1,145 proband specimens were sent for resequencing. More than half (4,217) of the 8,190 probands had trio specimens, and of these, 1,246 trio specimens were sent for whole exome sequencing.

FIGURE 1: PROBAND ACCRUAL AND TARGETS BY QUARTER AS OF 07/27/14



Actual Accrual and Targets by Quarter

	2010	2011				2012				2013				2014				2015		
	Dec	Mar	Jun	Sep	Dec	Mar	Jun	Sep	Dec	Mar	Jun	Sep	Dec	Mar	Jun	Sep	Dec	Mar	Jun	Sep
Target/Quarter	50	320	420	520	550	560	560	570	570	570	570	570	570	570	570	570	570	570	570	180
Target Cumm.	50	370	790	1310	1860	2420	2980	3550	4120	4690	5260	5830	6400	6970	7540	8110	8680	9250	9820	10000
Actual/Quarter	121	547	673	700	557	649	715	605	548	490	517	504	561	592	644	179				
Actual Cumm.	121	668	1341	2041	2598	3247	3962	4567	5115	5605	6122	6626	7187	7779	8423	8602				

Accrual Assessment Summary

Assessment Period	Target	Actual	Actual as % of Target
25% of Accrual Period Assement: Dec 11	1860	2598	140%
50% of Accrual Period Assement: Mar 13	4690	5605	120%
75% of Accrual Period Assement: Jun 14	7540	8383	111%

TABLE 1: PROBAND DEMOGRAPHICS AND ANATOMIC DIAGNOSIS AS OF 07/27/14

	Mean±SD / N(%)
Number of probands	8602
Age	10.4±12.6
Median (IQR)	5.5 (0.5 ,16.6)
Age group	
<1 year	2757 (32.1%)
1 - 12 years	2981 (34.7%)
13 - 18 years	1202 (14.0%)
>19 years	1662 (19.3%)
Race	
White	6426 (78.3%)
Black	660 (8.0%)
Asian	517 (6.3%)
Other	609 (7.4%)
Hispanic	
Yes	1950 (23.2%)
No	6438 (76.8%)
Abnormal extracardiac findings	
Yes	2643 (31.9%)
No	5631 (68.1%)
If yes, clinical genetic testing performed*	1054 (39.9%)
Abnormal karyotype	
Yes	271 (20.6%)
No	1043 (79.4%)
Abnormal microarray results	
Yes	217 (29.5%)
No	518 (70.5%)

TABLE 1: PROBAND DEMOGRAPHICS AND ANATOMIC DIAGNOSIS AS OF 07/27/14

	Mean±SD / N(%)
Abnormal FISH results	
Yes	120 (18.6%)
No	524 (81.4%)
Cardiac diagnosis	
Form F100 (Enrollment form)	8602
Atrial septal defect	956 (11.1%)
Conotruncal defect	3864 (44.9%)
Left-sided obstructive lesion	1727 (20.1%)
Heterotaxy syndrome	573 (6.7%)
Form F106 (Fyler codes)	7564
Tetralogy of Fallot	1141 (15.2%)
Double outlet right ventricle	440 (5.9%)
Atrial septal defect - Secundum	1708 (22.8%)
Hypoplastic left heart syndrome	382 (5.1%)
Coarctation of the aorta	911 (12.2%)
D-transposition of the great arteries	714 (9.5%)
Isolated ventricular septal defect	2116 (28.2%)
Atrioventricular canal	702 (9.4%)
Heterotaxy/Related Findings (F105, F106)	570 (7.6%)

**Amongst the 2643 patients with extracardiac findings, 810 (31%) had karyotyping, 378 (14%) had FISH and 467 (18%) had Microarray testing.*

TABLE 2: PROBAND CARDIAC DIAGNOSIS BY AGE GROUP AS OF 07/27/14

	< 1 year	1 - 18 years	>19 years
N	2757	4183	1662
Primary Cardiac Diagnosis (F100)	**2757**	**4183**	**1662**
Atrial septal defect	4.8%	15.9%	9.6%
Conotruncal defect	53.2%	37.8%	49.0%
Left-sided obstructive lesion	19.6%	21.2%	18.1%
Other	22.5%	25.1%	23.3%
Heterotaxy Syndrome	7.3%	6.2%	6.9%
Fyler Coding (F106)	**2336**	**3714**	**1514**
Tetralogy of Fallot	17.4%	11.8%	20.2%
Double outlet right ventricle	6.4%	5.8%	5.2%
Atrial septal defect - Secundum	24.7%	24.4%	16.0%
Hypoplastic left heart syndrome	7.3%	4.9%	2.1%
Coarctation of the aorta	14.7%	12.0%	8.5%
D-transposition of the great arteries	9.6%	8.3%	12.4%
Isolated ventricular septal defect	36.4%	24.9%	24.0%
Atrioventricular canal	12.2%	9.2%	5.3%
Heterotaxy/Related Findings	7.5%	8.0%	6.6%