University of California

Larry L. Sautter Award Submission

**Epilepsy Phenome Genome Project -
Pharmacogenomics Research Informatics at the University
of California, San Francisco**
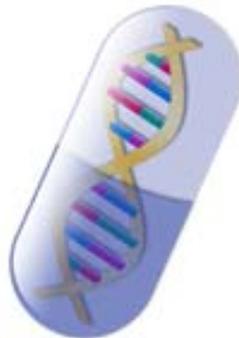
Date: March 19th, 2009

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1. Project Title

Epilepsy Phenome Genome Project - Pharmacogenomics Research Informatics at the University of California, San Francisco

2. Submitters' Details

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3. Names of Project Leaders and team Members

Informatics Project Team
Mr. Gerry Nesbitt, MBA PMP
Director of Bioinformatics, UCSF

Mr. Kevin Miller
Data Manager and Senior Developer, UCSF

Mr. Alan Carpenter
Senior Developer, UCSF

Mr. Harry LeBlanc
Senior Data Architect (Contract), UCSF

Project Sponsors
Dr. Brian K. Alldredge, Pharm.D.
Professor of Clinical Pharmacy & Neurology Associate Dean, Academic Affairs, School of Pharmacy University of California, San Francisco

Mr. Michael Williams, MA
Chief Information Officer, EPGP

Dr. Daniel Lowenstein, M.D.
Department of Neurology at UCSF, Director of the UCSF Epilepsy Center

Ruben Kuzniecky, M.D.
Professor of Neurology, Comprehensive Epilepsy Center, NYU Medical Center

Margaret Jacobs
Program Director, NIH/NINDS Extramural Research Program, Neuroscience Center

4.   Project Significance

In May 2007, a team of US scientists at 15 epilepsy centers led by UCSF and NYU received a grant of $15M to study the complex genetic factors that underlie some of the most common forms of epilepsy. The study, known as the "Epilepsy Phenome/Genome Project" (EPGP), is funded by the National Institute of Neurological Disorders and Stroke, and brings together over 50 researchers and clinicians from 15 medical centers around the country.

Epilepsy is one of the commonest neurological disorders. Although multiple antiepileptic drugs (AEDs) are available, treatment in individual patients is often problematic due to the unpredictability of efficacy, adverse drug reactions, and optimal dosage. Moreover, up to one third of patients develop drug refractory epilepsy despite optimal treatment. With the development of EPGP's pharmacogenomic data capture and reporting tool, UCSF is paving the way for a more systematic application of pharmacogenetics in the field of epilepsy, helping to understand some of the genetic influences on pharmacoresistance. This research may one day enable pharmacogenetic testing in patients to be used to tailor AED therapy - the era of personalized medicine.

This pharmacogenomics research informatics data capture and reporting tool is truly innovative. As far as we are aware, there is no other web-based informatics tool available for the purposes of phenotyping responses to AED medications. The tool allows the data to be captured across 15 EPGP clinical sites as efficiently as possible simply using an Internet browser. This tool can be shared with others who may be interested in learning about the workflow codified and data elements captured in this tool. This project demonstrates collaboration across UCSF (EPGP, School of Pharmacy, Human Genetics) and with many external universities/organizations. To date, detailed AED drugs histories of over 200 EPGP subjects has been gathered using this tool. This data will become an immense source of new and exciting knowledge in the near future, resulting in better treatments for epilepsy.

5. Project Description

5.1. What is EPGP?

UCSF received a grant of $15M to study the complex genetic factors that underlie some of the most common forms of epilepsy. The study, known as the "Epilepsy Phenome/Genome Project" (EPGP), is funded by the National Institute of Neurological Disorders and Stroke, and brings together over 50 researchers and clinicians from 15 medical centers around the country. The EPGP study is being led by UCSF's Dr. Daniel H. Lowenstein. Dr. Lowenstein is Professor and Vice Chairman in the Department of Neurology at the University of California, San Francisco (UCSF), Director of the UCSF Epilepsy Center, and Director of Physician-Scientist and Education Training Programs for the UCSF School of Medicine. He was also a recent president of the American Epilepsy Society. Dr. Lowenstein was instrumental in establishing and nurturing the vision for the EPGP study to help further his life-long commitment to discovering better therapies and new cures for epilepsy.

The Epilepsy Phenome/Genome Project (EPGP) is a large-scale, national, multi-institutional, collaborative research project aimed at advancing our understanding of the genetic basis of the most common forms of idiopathic and cryptogenic epilepsies and a subset of symptomatic epilepsy; i.e. epilepsies that are probably related to genetic predispositions or developmental anomalies rather than endogenous, acquired factors such as CNS infection, head trauma or stroke. The overall strategy of EPGP is to collect detailed, high quality phenotypic information on 3,750 epilepsy patients and 3,000 controls, and to use state-of-the-art genomic and computational methods to identify the contribution of genetic variation to: 1) the epilepsy phenotype, 2) developmental anomalies of the brain, and 3) the varied therapeutic response of patients treated with AEDs.

5.2. What is Pharmacogenomics?

Genetic variability has recently been implicated in the development of familial epilepsy syndromes and in heterogeneous responses of epilepsy patients to drug treatment. Mutations in distinct proteins have been shown to underlie the development of epilepsy, increase propensity for drug resistance, and alter drug metabolism. Improved understanding of how individual genetic variability may alter the efficacy of pharmacological therapeutic interventions is an important and timely goal. The investigation of relationships between genotype and patient responses to drug treatment is termed **pharmacogenomics**.

5.3. Pharmacogenomics and Epilepsy

Although epilepsy is one of the most common neurological disorders and it is known that genetic factors play a role in response to antiepileptic drug (AED) treatment, the study of the pharmacogenetics of epilepsy has received relatively little attention and has not resulted in clinical applications to date. EPGP's improved understanding of the pathogenesis of epilepsy and the mechanism of action of AEDs, together with recent advances in genetics and decreasing genotyping costs, have now paved the way for a more systematic application of pharmacogenetics in the field of epilepsy. It is hoped that the resulting knowledge will lead to a more rational treatment of epilepsy, development of more efficacious AEDs, and facilitation of clinical trials of new AEDs.

5.4. EPGP's Contribution to Pharmacogenomics and Epilepsy

The EPGP will provide an excellent patient population to address the significance of genetic contributions to AED pharmacoresistance. The rigorous collection of drug response data, careful assignment of pharmacosensitive (PS) or pharmacoresistant (PR) phenotypes, and a large sample of patients will provide significant power to detect clinically meaningful associations between genetic polymorphisms and AED resistance. Furthermore, the proposed whole-genome analysis will allow us to consider novel drug response genes and is likely to significantly enhance our understanding of the biology of AED response.

In addition, the EPGP will establish a national resource that will be available to other researchers who will apply new analytical methods in the future that are impractical or unimagined today. The Epilepsy Phenome/Genome Project engenders the prospect of major advances in epilepsy research that will ultimately be of direct benefit to patients. Targeted AED therapy that recognizes individual patient response through pharmacogenomics is a promising future for the treatment of epilepsy.

5.5. Need and Relevance for Pharmacoresistance Data Collection

Need for Pharmacoresistance Data Collection
The underlying abnormality and a wide variety of modifying factors for a given subject are likely to influence whether or not the subject responds to a given medication. Despite the availability of a relatively large number of anticonvulsant drugs, there appears to be a fairly limited spectrum of pharmacologic mechanisms of action of these drugs, and they all carry the risk of a number of side effects, especially related to normal cognitive function.

Relevance for Pharmacoresistance Data Collection
Recent genetic association studies have identified AED resistance as a phenotypic characteristic that could be used to identify genetically homogenous subgroups for analysis.

5.6. AED Classification Decision Tree

The study coordinator at the clinical site will use the decision tree below to classify the AED. This diagram leads the coordinator through a series of decision points and will ultimately lead you to the AED classification of uninformative, success or failure.
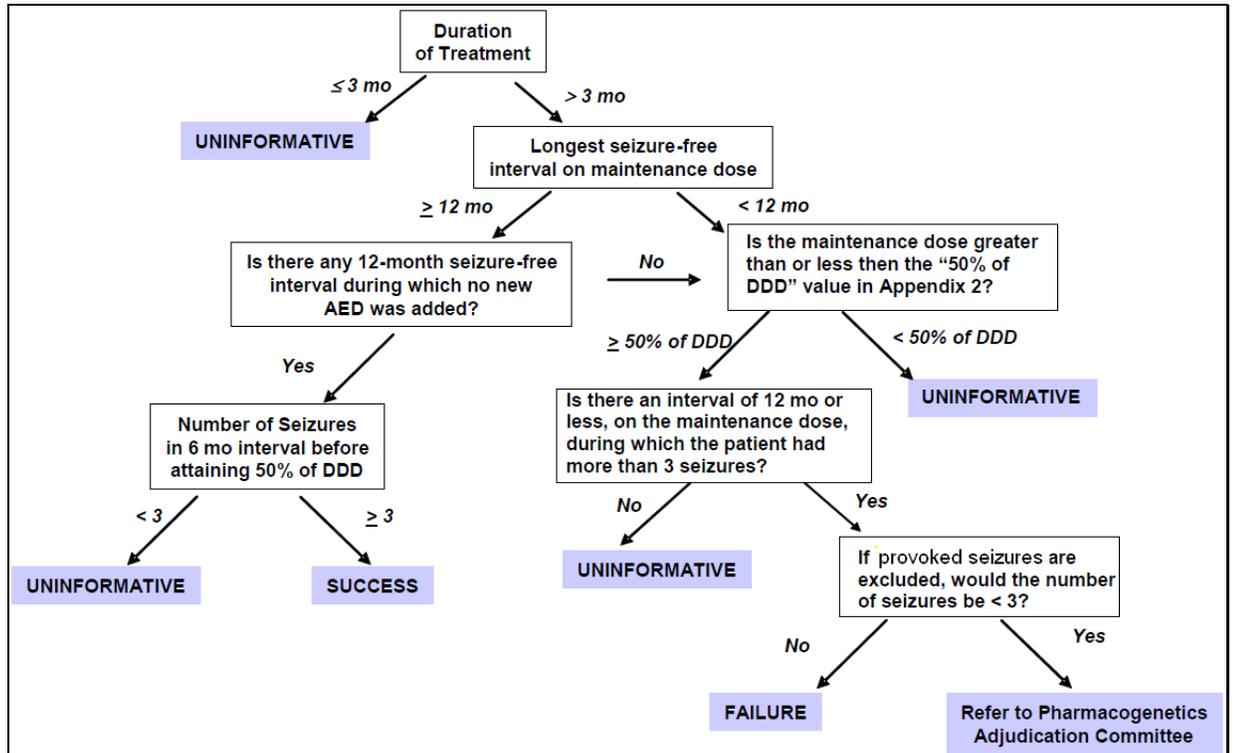

Fig. 1 – Pharmacoresistance Decision Tree
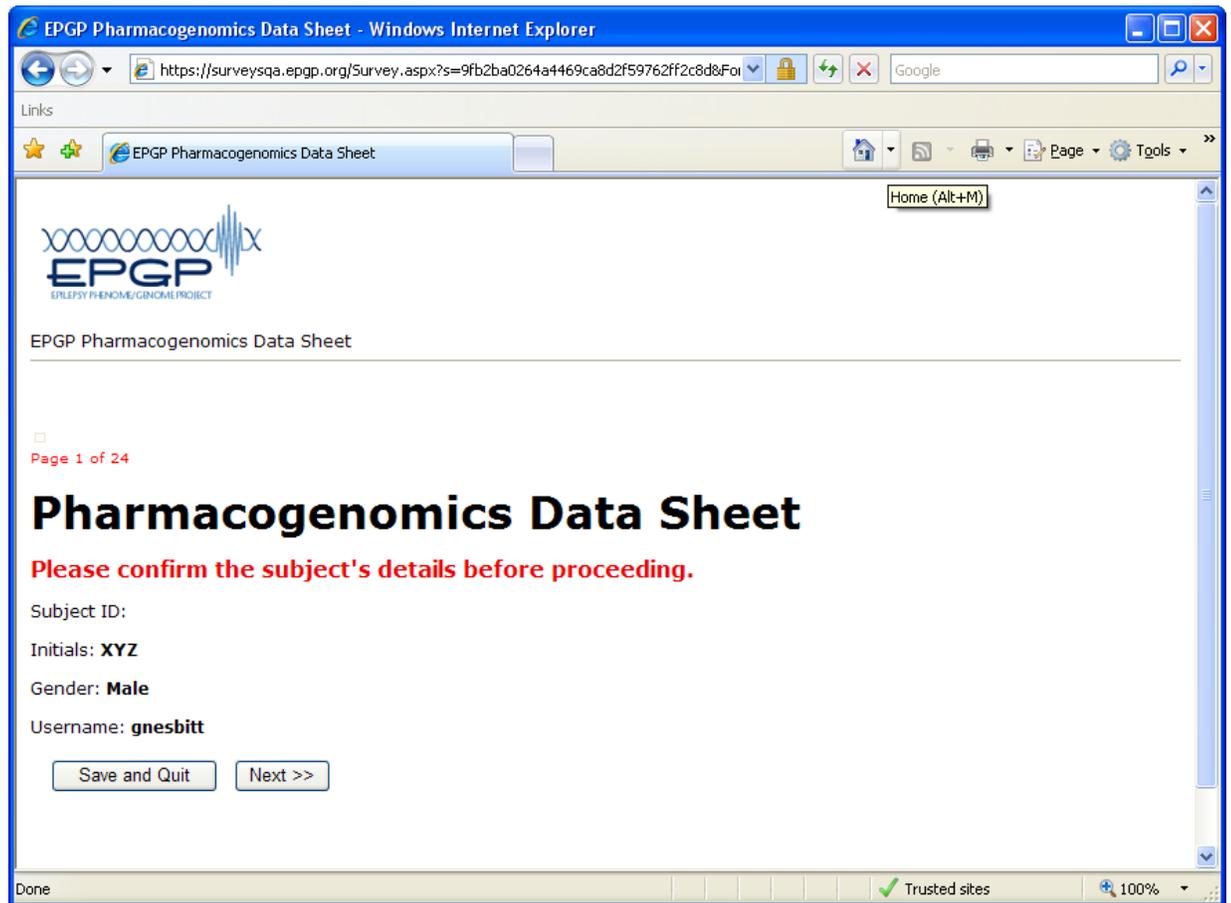
5.7. Sample AED Worksheet

The study coordinator will examine the patient's medical files to compile the AED history for the patient using an AED worksheet. This worksheet will then serve as an input document to the Pharmacogenomics Data Sheet.

AED	Date started (month/year)	Date stopped (month/year) or "Ongoing"	12-month seizure free interval? (Y/N)	Classification (to be filled in below after using the "Decision Tree" diagram)
1. Phenobarbital	1/84	5/99	N	failure
2. Phenytoin	3/88	3/99	N	failure
3. Carbamazepine	2/99	6/01	N	failure
4. Valproate	7/99	ongoing	Y	uninformative
5. Gabapentin	4/03	8/03	N	---
6. Topiramate	5/05	5/06	N	---
7. Levetiracetam	5/06	ongoing	Y	success

5.8. Pharmacogenomics Data Sheet (Data Capture)

The Pharmacogenomics Data Sheet form captures up to 1430 data points for each subject (study participant). The web-based form guides the study coordinator through the AED data capture process, enforcing rigorous data validation and skipping irrelevant questions based on previous answers.

Subject Confirmation Page

Patient Level Data - # Epileptic Seizures Prior to AED Treatment

Patient Level Data - # AEDs Tried, Epilepsy Surgery and VNS Placement

Patient Level Data – ACTH Treatment of Infantile Spasms

Patient Level Data – Ketogenic Diet

Pharmacogenomic Worksheet

AED-level data Sheet – AED #1

AED-level data Sheet – AED #1

Browser window showing EPGP Pharmacogenomics Data Sheet:
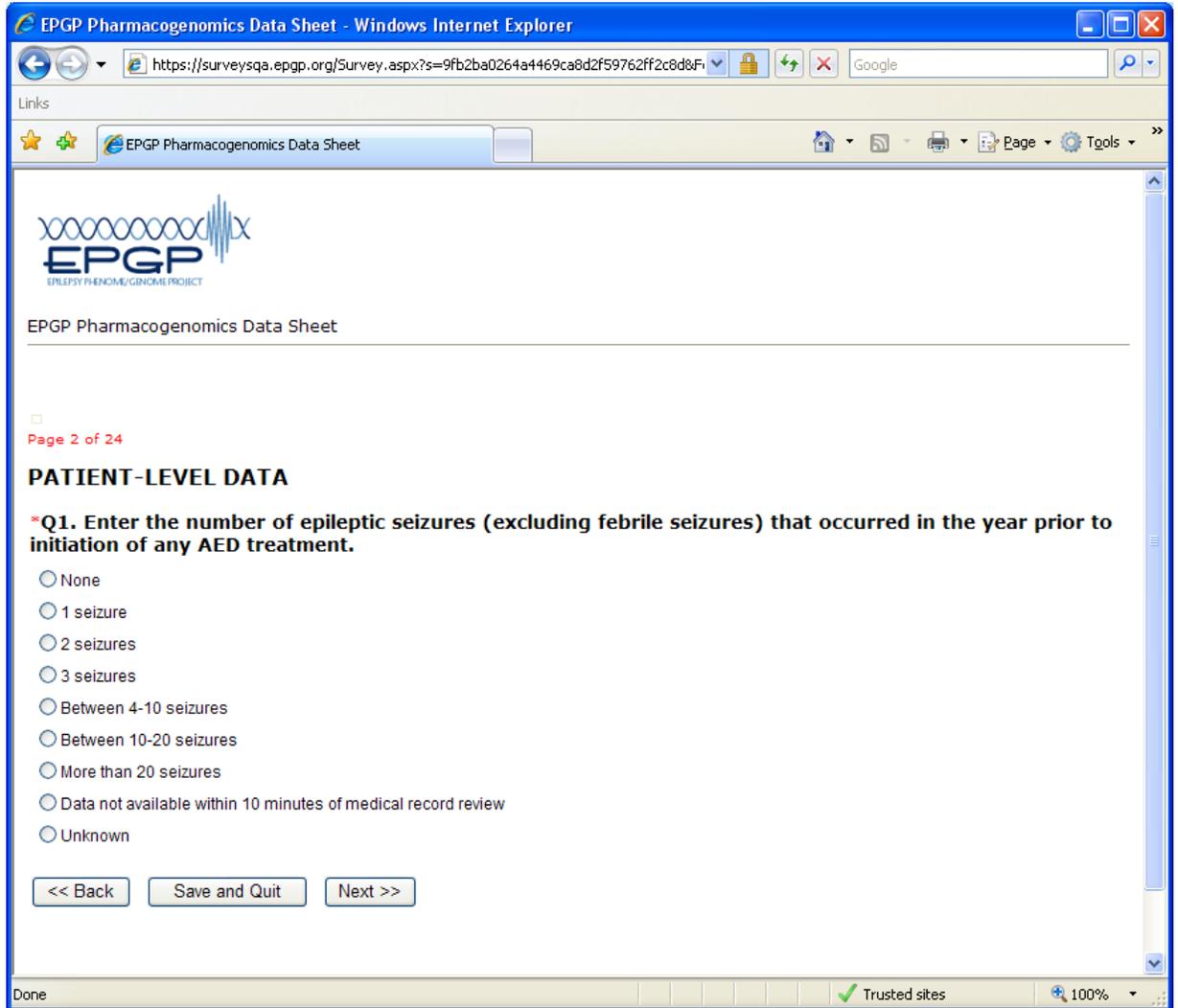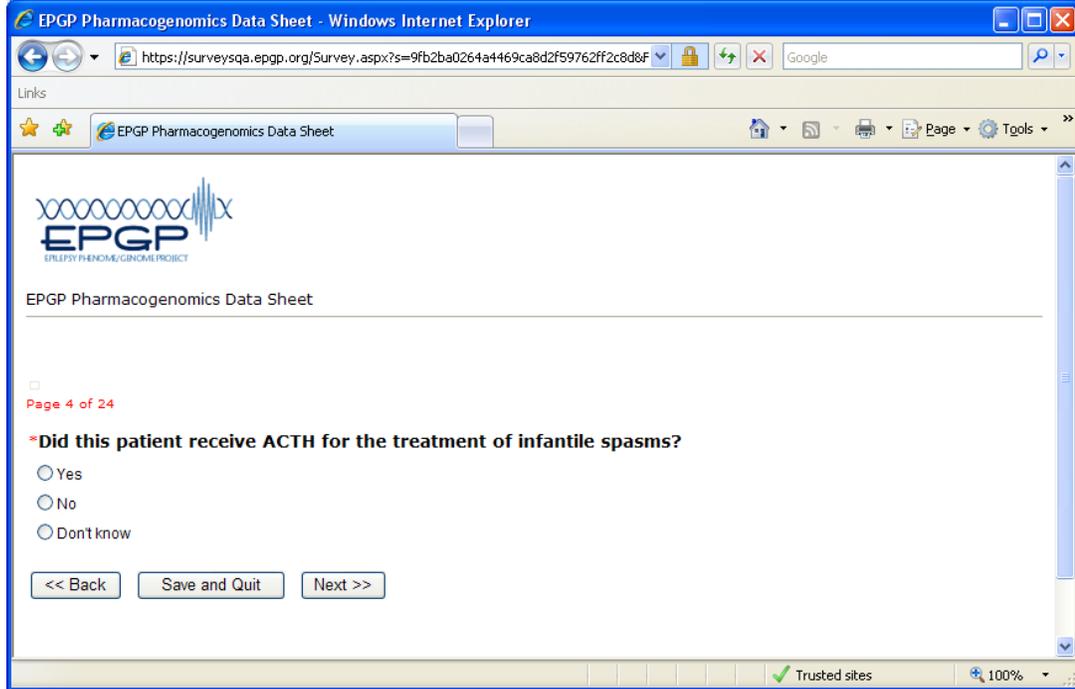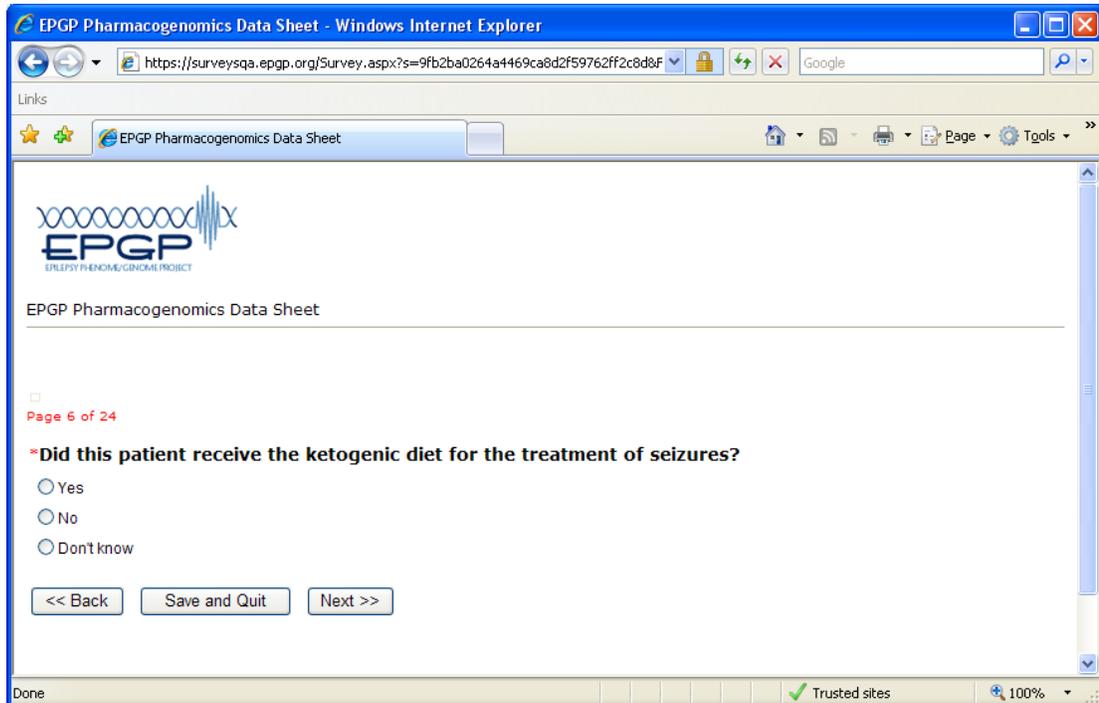
URL: https://surveysqa.epgp.org/Survey.aspx?s=9fb2ba0264a4469ca8d2f59762ff2c8d&ForceNew=true&SID=EPGP01845&Initials=X\

EPGP Pharmacogenomics Data Sheet

AED-Level Data

AED #1 : Clonazepam (Klonopin)

*Q4. Dose Information - Clonazepam (Klonopin)
"Maintenance dose" is defined as the dose taken by the patient during the longest seizure-free interval.

	*Maximum total daily dose achieved (-9=NK)	*Dose Units	Maintenance Dose (if less than max.)	Dose Units	*Select the source of information that you most relied upon to answer these queries:
AED	250	mg/day	200	mg/day	Medical records of patient under your care

*Q5. Is there a documented AED blood level on the maintenance dose?
If there are multiple blood levels available, please choose the blood level value that appears to reflect good AED adherence and is closest to a median value - e.g., if patient has blood levels of 15, 1, 18 and 16 mg/L on the maintenance dose - then, you might decide to disregard the level of 1 (probable nonadherence) and would then choose to enter "16" below since it is between the remaining high (18) and low (15) values.

	*Documented AED blood level?	[IF YES] Value of AED blood level on the maintenance dose (mcg/mL)
AED	Yes	500

*Q.6 Was this AED suspected (either by you or the treating provider) to have caused any toxicity event(s) that led to hospitalization or an emergency department visit?

◉ Yes
◯ No

Q6A. If this AED was suspected (either by you or the treating provider) to have caused any toxicity event(s) that led to hospitalization emergency department visit, please provide details:
NOTE: Type of Toxicity >> Hypersensitivity/systemic (2 or more of the following features: fever, skin rash, hepatitis, organ failure, eosinophilia)

	Month	Year (yyyy) [9999 for NK]	AED Dose at time of admission	AED dose units	AED blood level (mcg/mL)	Did the provider of care suspect this AED as the causative agent?	Do you concur?	Type of Toxicity
Hospitalization Event #1	Feb	1985	400	mg/day	500	No	Yes	GI (nausea, vomiting, pain)
Hospitalization Event #2	Select:			Select:		Select:	Select:	Select:
Hospitalization Event #3	Select:			Select:		Select:	Select:	Select:
Hospitalization Event #4	Select:			Select:		Select:	Select:	Select:
Hospitalization Event #5	Select:			Select:		Select:	Select:	Select:

AED-level data Sheet – AED #1…continued….

Q6B. At the time of the hospital/ED events listed above, was the patient taking any of the interacting drugs listed on the list of interact
YOU'LL NEED TO REFER TO THE LIST OF NON_AEDS LISTED AFTER THIS QUESTION.

	Non-AED #1 Generic Drug Name	Enter the month/year started and month/year ended, e.g. 03/2002 to 07/2002.	Non-AED #2 Generic Drug Name	Enter the month/year started and month/year ended, e.g. 03/2002 to 07/2002.	Non-AED #3 Gener Name
Hospitalization Event #1					
Hospitalization Event #2					
Hospitalization Event #3					
Hospitalization Event #4					
Hospitalization Event #5					

Non-AED Generic Drug	Brand name Drug

Q7. Reason for discontinuation
AE Note: Hypersensitivity/systemic (2 or more of the following features: fever, skin rash, hepatitis, organ failure, eosinophilia)

	Reason (Check all that apply)			If NOT Tolerated, select the adverse effect from the list below:	IF OTHER, please specify.
	Recurrent seizures	Not tolerated	Unknown		
AED	☑	☐	☐	Renal calculus ▾	

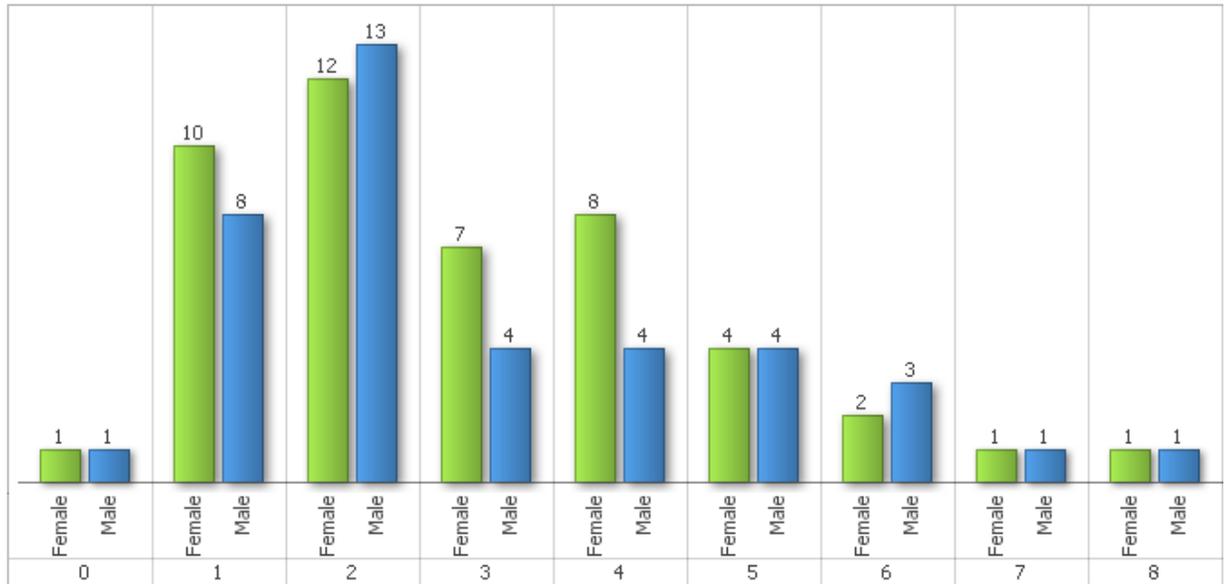**Q8. Blood level on the dose taken at time of discontinuation: (mcg/mL)**

500

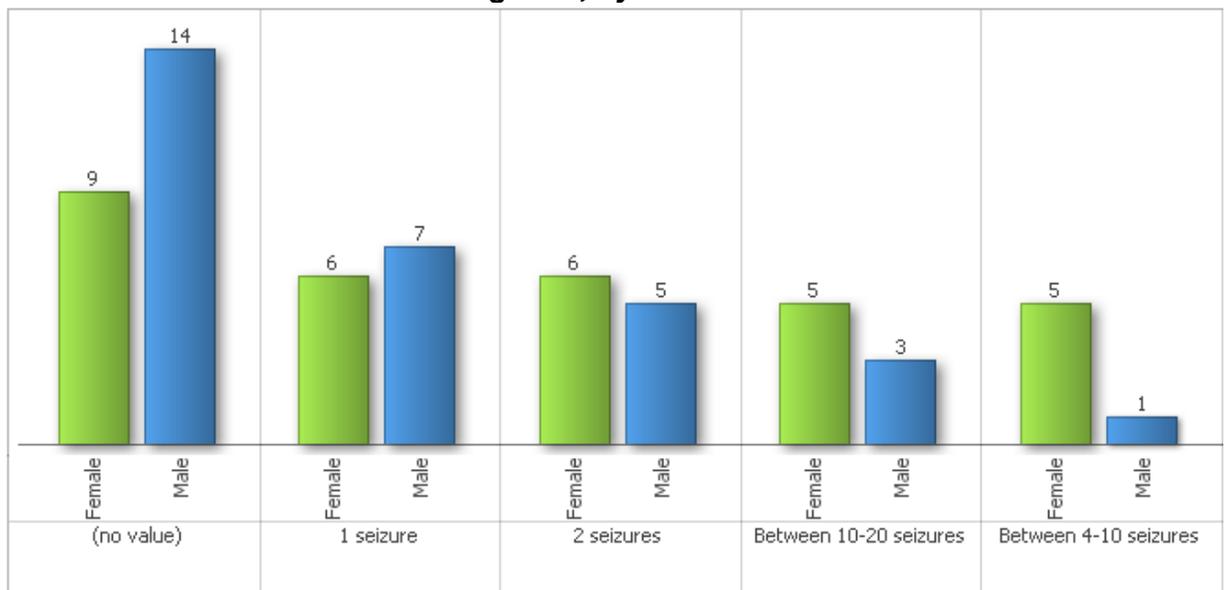[<< Back] [Save and Quit] [Next >>]

Done   ✓ Trusted sites   🔍 100% ▾

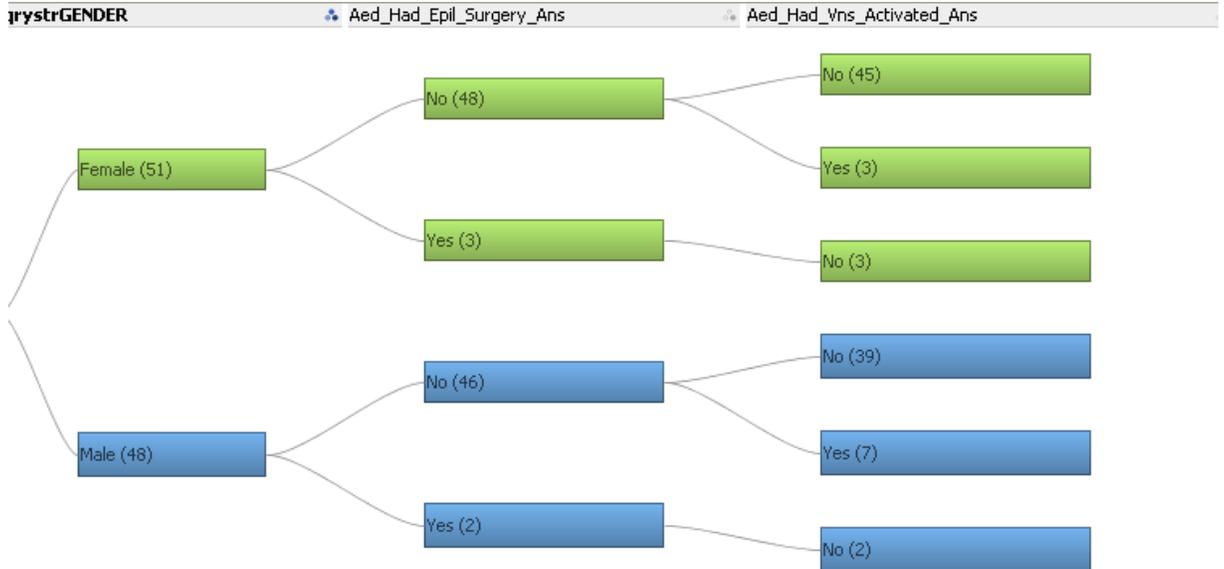### 5.9. Pharmacogenomics Analysis & Reporting (Examples)

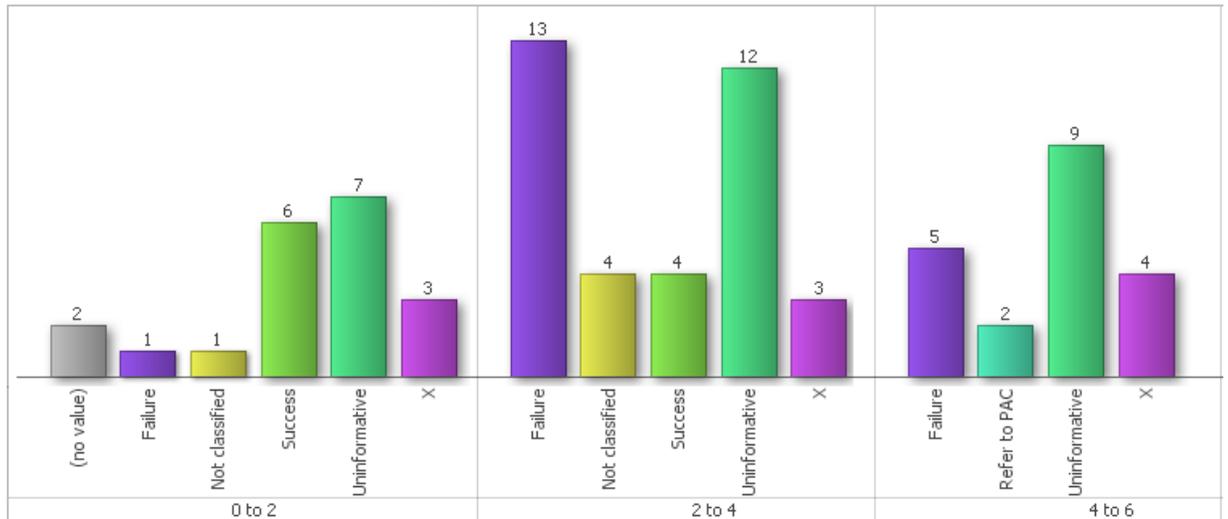*Number of AEDs Tried by Gender*

Number of Seizures Prior to taking AED, by Gender

Number of Patients that had Epilepsy Surgery and had VNS Activated, by Gender.

Classification of First AED by Number of AEDs Tried

6.   Feedback from Stakeholders

Person: Brian Alldredge, PharmD

"*Currently, 30% of persons with epilepsy fail to respond to first-line epilepsy drug therapies. Genetic factors appear to influence drug response – as demonstrated by numerous pharmacogenetic studies in epilepsy – but, there is tremendous variability in study results. For example, there are 8 positive studies and 7 negative studies of the association between polymorphisms in the human multidrug resistance (MDR1, ABCB1) gene and antiepileptic drug resistance. Some of this variability is thought to be related to inconsistent criteria used to assign clinical phenotypes (i.e., drug 'successes' and drug 'failures'). EPGP, and the pharmacogenomic phenotyping efforts described here, represent a critical step in the clear, unambiguous assignment of drug response phenotypes. This will lead us to an improved understanding of the genetic factors that influence drug response – and, hopefully, toward improvements in the safe and effective use of antiepileptic drug use in all patients.*"