Incorporating genetic data on PCOR studies: building a road map for stakeholder engagement

PCORI-EAIN 2419 Presentation #3

Principle Investigator:
Zohreh Talebizadeh, PhD

Outline

- Overview of the previous PowerPoint presentation (PPT#2)
- Results of the PPT#2 evaluation survey
- Additional patient/parent personal stories
- Examples of published epidemiological/patient outcomes studies done by including genetic information
- Examples of genetic research done by our CAB members (Scientists) in relation to patient outcomes
- Project website-Update
- What is next? Collecting participants' feedback!

Introduction

- Our overall goals are to:
  - (1) Assess IF it is possible to use genetic information to improve patient health outcomes and
  - (2) If YES, then HOW can this be achieved?
- In the PPT#2, we reviewed several patient/parent stories, and briefly described the concepts of genetics and Precision Medicine Initiative.
- In the PPT#3:
  - The results of the PPT#2 evaluation survey will be shared.
  - Additional patient/parent stories will be reviewed.
  - Examples of research done by our CAB members (Scientists) or from literatures, related to the objective of this Engagement project, will be reviewed.

PPT#2 Evaluation Survey-Results

32/33 members responded =97%

For the following statements, please indicate to what extent you disagree or agree with "0" indicating "strongly disagree" and "10" indicating "strongly agree". There are no right or wrong answers, it is important that the responses reflect your individual experience and opinions.

1. "The information in the PPT#2 presentation was provided in an easy to understand manner"	**Rating Average**	**Response Count**
	9.03	**32**
	answered question	**32**

2. "The overview of the concept of genetics was provided in an easy to understand manner"	**Rating Average**	**Response Count**
	8.75	**32**
	answered question	**32**

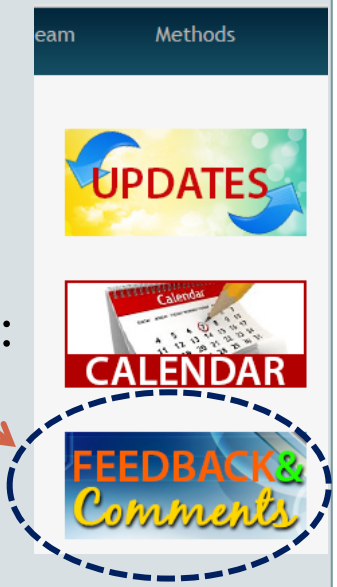
3. "The information about Precision Medicine Initiative was provided in an easy to understand manner "	**Rating Average**	**Response Count**
	9.16	**32**
	answered question	**32**

4. "Patient personal stories were informative and provided in an easy to understand manner"	**Rating Average**	**Response Count**
	9.41	**32**
	answered question	**32**

5. Would you like to schedule a personal meeting and/or call with the PI for further clarification of materials discussed in the PPT #2 presentation?	**Response %**	**Response Count**
Yes, I would like to schedule a meeting	**6.3%**	**2**
No, not at this point	**93.8%**	**30**
	answered question	**32**

Feedback & Comments

- To see all Feedback & Comments received from our participants please visit the project website:
  - http://genetics-outcomes.net/EAIN/feedback.html



- Feedback & Comments are listed by the following categories:
  - Meeting#1 presentation (PPT#1)
  - Meeting#2 presentation (PPT#2)
  - Project website
  - Memorandum of Agreement (MOA)
  - Suggested structure for the meetings
  - Selection of topics to be covered during the course of this project
  - Overall comments/suggestions

PPT#2 Group Discussion

- In response to some members' feedback we decided to have a brief group discussion with local members, after sending out each presentation, to collectively review the presentation and project progress. If you are interested to participate, please let us know.
- Our PPT#2 group discussion was held on 4/19/2016 with a number of our local members (n=14).
- Group discussion notes are posted on the website.

Meeting 2 agenda (took place via email on April 8, 2016)

- Overview of the PowerPoint (PPT) presentation #1
- Results of the PPT#1 evaluation survey
- Introduction to the concept of genetics
- Overview of the Precision Medicine Initiative (PMI)
- Presentations of patient/parent personal stories
- Project website-Update
- What is next?

Meeting 2-PowerPoint Presentation (PPT#2)
Meeting 2-Group Discussion
Meeting 2-Evaluation Survey

PPT#2 group discussion
Sorry!
We forgot to take a picture

Patient/Parent Stories

- In this section our patient/parent representatives continue to share their personal stories and why they are interested in genetic information.

- Please note that
  - Our Engagement project is not focused on any specific disease. We would be happy to add more patient stories in our future presentations, please feel free to send us your story!

  - All the stories are provided for educational purpose only. We do not approve or disapprove, or otherwise assess any health care choices shared in the personal stories.

Patient Story 6: (Kelly Ranallo)

- My daughter, Allie, was diagnosed at the age of 8 with mosaic Turner Syndrome (TS) - 45XO 46XX - approximately 80% normal cells and 20% TS cells.

- Her first medication complication was noted following a foot surgery for Bilateral Brachimetarsia. She experienced poor recovery from anesthesia with extreme nausea and hallucinations. She also experienced poor pain management with use of Oxycodone and Oxycontin.

- Despite continued reports that her pain was better controlled with Tylenol and or Advil the nursing staff and physicians kept telling her it wasn't possible and she just had a low pain tolerance and implied drug seeking behaviors.

Patient Story 6 (Cont.): Drug Side Effects

- During this same period, she was started on hormone replacement for suspected premature ovarian failure related to the TS diagnosis. After the initiation of Estrogen she has extreme complication of prolonged heavy bleeding and therefore was started on Progesterone to help regulate her cycles.

- While on the Progesterone she reported significant dizziness and feeling as if she was going to pass out, often requiring her to come home from school on a daily basis.

- When this was reported to her provider the response was "*have her take it at night that way she will sleep through the side effects and it won't impact her school schedule*".

Patient Story 6 (Cont.): Genetic Testing

- Not content with that solution we self-referred to a Personalized Medicine clinic to undergo genetic testing to assess her drug metabolism. The molecular genetics results reported findings for two genes (called CYP2C19 and CYP2D6), involved in regulating drug metabolism.

- The following is a more technical description of this genetic finding:
  - *2*2 genotype on the CYP2C19 resulting in a poor metabolizer of this drug pathway (Progesterone included) and
  - *1/*2A genotype on the CYP2D6 which is associated with a ultra rapid metabolizer (Oxydontin included)

Patient Story 6 (Cont.): Impact of the Genetic Testing

- We were glad that her genetic finding confirmed her symptomatic reporting.
- Although the information is not 100% predictable for all drug metabolism, it did empower us to help her make better decisions on what drugs might be toxic to her as well as which one provided her a better outcome when she needed pain management for future surgeries.
- YouTube link: Hope, A Parents Perspective (Interview with Kelly Ranallo): https://www.youtube.com/watch?v=axCmVaWrolY

Example:
How Genetic Testing Was Helpful in Managing Allie's Care?

- Most recently she was started on anti-anxiety medication (Lexapro). When the first increase in dosing had significant side effects, we produced her drug metabolism report to demonstrate the prescribed drug was classified as a poor metabolized drug for her. This report included a series of tables showing which drugs are being metabolized by these two genes (see examples in the next slides).

- As a result, her provider made an immediate change in the dosing that typically they would not make for a 4-6 week "adjustment" period and she stabilized on the drug in under a week.

- This genetic information has and continues to impact the outcome of Allie prescription drug management. It may not be perfected, but it has definitely impacted the overall outcome of her health and medical management.

Example: Genetic Testing Report
Drugs Metabolized by CYP2C19

Here is an example of a genetic testing report for drug metabolism genes. The below table and description were included in the patient report.

Table for Drugs and CYP2C19 Metabolism*		
Proton Pump Inhibitors	Anti-depressants	
esomeprozole (Nexium®), lansoprazole (Prevacid®), omeprazole (Prilosec®), pantoprazole (Protonix®), rabeprazole (Aciphex®)	amitriptyline (Elavil®), citalopram (Celexa®), clomipramine (Anafranil®), escitalopram (Lexapro®), imipramine (Tofranil®), sertraline (Zoloft®)	
Anti-epileptics	Oncology	
diazepam (Valium®), mephobarbital (Mebaral®), phenobarbital (Luminal®), phenytoin (Dilantin®), primidone (Mysoline®)	cyclophosphamide (Cytoxan®), nilutamide (Nilandron®), teniposide (Vumon®), thalidomide (Thalomid®)	
Hormone	Blood Pressure	
progesterone (Endometrin®)	propranolol (Inderal®)	
Pain Treatment	Anti-infective	
carisoprodol (Soma®), indomethacin (Indocin®)	chloramphenicol (AK-Chlor®), proguanil (Malarone®)	
Anti-retroviral	Blood thinner/Anti-platelet	
nelfinavir (Viracept®)	Warfarin (Coumadin®)	Produg: clopidogril (Plavix®)

*This table contains examples of medications that can be affected by mutations in the CYP2C19 gene. Care should be taken with all medications and a conversation should occur between the patient and the provider to ensure up-to-date information is assessed prior to prescribing any medication.

Example: Genetic Testing Report
Drugs Metabolized by CYP2C6

Here is an example of a genetic testing report for drug metabolism genes. The below table was included in the patient report.

Table for Drugs and CYP2D6 Metabolism*	
Antidepressants	Antipsychotics
amitriptyline (Elavil®), clomipramine (Anafranil®), desipramine (Norpramin®), duloxetine (Cymbalta®), fluoxetine (Prozac®), fluvoxamine (Luvox®), imipramine (Tofranil®), nortriptyline (Pamelor®), paroxetene (Paxil®), sertraline (Zoloft®), venlafaxine (Effexor®)	Haloperidol (Haldol®), perphenazine(Trilafon®), riseridone (Risperdal®), chlorpromazine (Thorazine®), thioridazine, zuclopenthixol, aripiprazole (Abilify®), thioridazine (Mellaril®)
Antihypertensives	Antiarrythmics
Diltiazem(Cartia®), carvedilol (Coreg®), metoprolol (Toprol®), propranolol (Inderal®)	Propafenone, encainide, flecainide (Tambocor®), lidocaine, mexiletine
Pain Treatment	Gastrointestinal
Oxycodone (Oxycontin®) Lidocaine (Lidoderm®) / Prodrugs: Codeine, Tramadol (Ultram®)	Metoclopramide (Reglan®), ondansetron (Zofran®), promethazine (Phenergan®),
Cough, Cold, Antihistamine	Oncology
Dextromethorphan, chlorpheniramine	Prodrug: Tamoxifen (Nolvadex®)
Other:	
Amphetamine, atomoxetine (Straterra®), timolol (Timoptic®)	

Genetic Data and the Potential Application in PCOR Studies

- In this section, we are providing a few examples of genetic research done by our Scientific CAB members as well as published epidemiological/patient outcomes studies done by including genetic information. The purpose of sharing these materials is to familiarize our study participants with some potential avenues on HOW including genetic information may improve patient health outcomes, which is the goal of our Engagement project.

- Please note that
  - All the examples are provided for educational purpose only. We do not approve or disapprove, or otherwise assess any approach taken or the results generated from those studies.
  - The provided examples may contain some technical information; however, we think those details and references were necessary to be included here to stimulate scientific thoughts.

Examples: Published Epidemiological/Patient Outcomes Studies Done by Including Genetic Information

- Genetic factors may play a role in predisposing patients to poor outcomes. Association with particular gene variants [single nucleotide polymorphisms (SNPs)] has been reported for different condition prognosis, treatment outcomes, and risk assessment, as shown in the next slide.

- The ultimate impact of these findings on outcomes remains to be studied; however, they show that adding genetic risk factors may have a potential to improving sub-typing, and finding high risk patient subgroups, who require closer follow up.

Examples: Reported SNPs Associated with Patient Outcomes (PubMed Search)

To view references, please click on the reference number.

Reference	SNPs	Gene(s)	Diagnosis/Conditions	Outcomes Type	Results
Ref 1	p.His268Tyr (802C>T, s7439366)	UGT2B7	Kidney transplantation	Risk prediction	May help identify patients with post-surgery complication risk
Ref 2	17 SNPs	Cluster in or near several genes including PKHD1, HTR1A, NMBR, and IGF1R	Roux-en-Y gastric bypass (RYGB)	Prediction of surgery result	Influence weight loss outcomes variation after RYGB
Ref 3	rs670 A/A	APOA1	Breast cancer	Risk prediction. Prevention of breast cancer occurrence and progression	A/A carriage showed poor post-surgery prognosis; Carriers may benefit from advanced monitoring
Ref 4	several SNPs	KIR2DS3, IL28B	HIV-1/HCV co-infection	Prediction of treatment response	Improve predicting treatment responsiveness
Ref 5	HLA SNPs, 57 non-HLA SNPs	Genetic risk heterodimer, HLA-DQ2 and DQ8	Coeliac disease (CD)	Risk prediction	HLA SNPs testing is already used clinically; Improved the identification of potential CD patients
Ref 6	rs4919510C>G	miRNA-608	Nasopharyngeal carcinoma (NPC)	Risk prediction	Predicts locoregional recurrence in radiotherapy-treated NPC patients
Ref 7	Y186C variant of rs115232898	DPYD	Various aggressive cancers	Prediction of treatment response	A predictive marker for toxic effects of a therapeutic agent in individuals of African ancestry
Ref 8	p53 codon 72 polymorphism	p53 pathway	Locoregionally advanced nasopharyngeal carcinoma	Disease development prognosis; potentially useful for prediction of high risk of poor disease outcome	An independent prognostic marker for the condition; analysis of SNPs in the p53 pathway may facilitate the identification of patients at high risk of poor disease outcome

Example: A Detailed Summary of Published Data

- Data from the multinational Global Registry of Acute Coronary events (GRACE) from more than 17000 patients was analyzed by Eagle et al (Reference) to predict risk score for 6–month postdischarge mortality for ACS (acute coronary syndrome) patients and develop a clinical application. Nine predictors for 6–month mortality were identified, among them lower systolic blood pressure, increase in initial serum creatinine level, and initial cardiac enzyme elevation.

- However, authors agree that inclusion of additional risk factors, such as genetic biomarkers, would further increase model discrimination. To try this possibility, the same group included a genetic risk factor (rs1333049) to their prediction model as an additional variable (Reference).

- Risk prediction model after inclusion of rs1333049 showed an increased probability (p=0.040) to correctly classify additional 5.93% of the patients. The authors concluded that inclusion of additional genetic risk factors could enhance risk prediction models for adverse outcomes following ACS.

Valerie Hu, PhD
Scientist CAB Member & Parent Representative

- My first and unexpected exposure to autism spectrum disorder (ASD) occurred almost 27 years ago when my 2-year old son, Matt, was diagnosed with pervasive development disorder-not otherwise specified (PDD-NOS). Back then (1989), there was almost no information in the medical literature about PDD-NOS, a disorder that fell under the autism spectrum, and the link to autism, often described as a devastating lifelong condition that requires continuous support, was scary.

- The first 13 or more years after Matt's diagnosis were spent mainly on pursuing the right educational program and trying a wide variety of medications, more than 20 in all with virtually no positive effects on core symptoms, but with many negative side effects.

Dr. Hu-Research Projects

- Feeling frustrated with the lack of information about the biology of autism that could inform more rational pharmacologic therapies, I redirected my research to autism about 11 years ago with a goal of uncovering the underlying molecular pathobiology of ASD that could lead to better and earlier diagnosis as well as ASD biology-based treatments.
- However, realizing the tremendous heterogeneity (variety) in the clinical symptoms manifested by those on the spectrum, my laboratory developed a strategy to subgroup individuals with autism according to similarity of clinical symptoms for large-scale genome-wide genomics analyses which included:
  - gene expression (the amount of products produced from a gene),
  - epigenetics (changes outside DNA sequences that may influence gene function), as well as genetics studies, which are described in over 18 research articles and reviews published since 2006 (References).

Dr. Hu-Research Projects (Cont.)

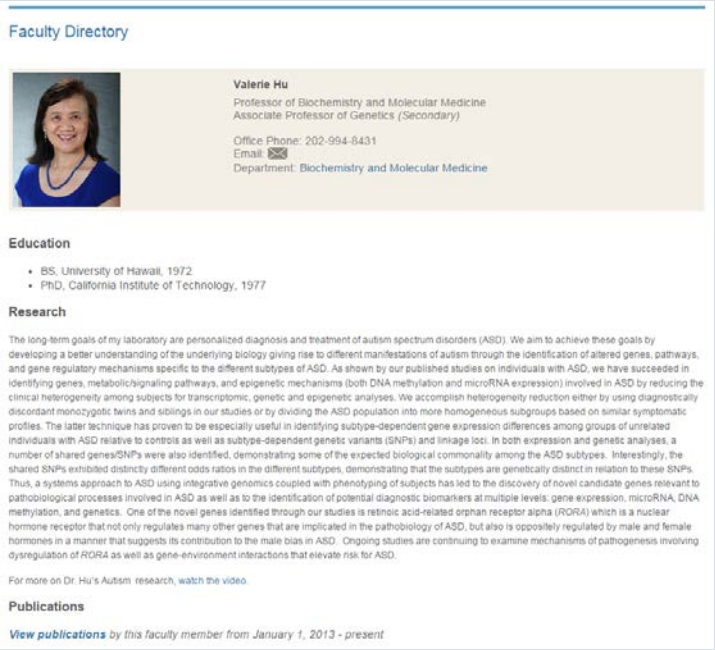
- Briefly, by subtyping individuals with ASD for gene expression and genetics analyses, we were able to describe subtype-dependent gene expression profiles that included both unique and overlapping genes and biological pathways associated with the different subtypes of ASD, and subtype-dependent genetic variants that may be used for diagnostic or pharmacogenomic applications.

- In collaboration with Dr. Zohreh Talebizadeh, we also identified subtype-dependent genetic linkage loci that were further stratified (subgrouped) to remove intra-familial genetic heterogeneity, leading to increased sensitivity to home in on genetic regions that may contribute to ASD in different families.

- Finally, data integration across multiple types of genomics analyses performed by my laboratory has led us to focus on gene-environment interactions involving a sex hormone responsive gene called *RORA*, which may contribute not only to the male bias in ASD, but also to elevated risk for autism by interaction with various chemicals that interfere with physiological hormone signaling.

Dr. Hu-Research Projects (Cont.)

- More information on my autism studies can be found in a YouTube video: https://www.youtube.com/watch?v=6sYRYzsS45Y
- and on my departmental website:
  http://www.gwumc.edu/smhs/facultydirectory/profile.cfm?empName=Valeri%20Hu&FacID=2046028605



Faculty Directory

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Education

- BS, University of Hawaii, 1972
- PhD, California Institute of Technology, 1977

Research

The long-term goals of my laboratory are personalized diagnosis and treatment of autism spectrum disorders (ASD). We aim to achieve these goals by developing a better understanding of the underlying biology giving rise to different manifestations of autism through the identification of altered genes, pathways, and gene regulatory mechanisms specific to the different subtypes of ASD. As shown by our published studies on individuals with ASD, we have succeeded in identifying genes, metabolic/signaling pathways, and epigenetic mechanisms (both DNA methylation and microRNA expression) involved in ASD by reducing the clinical heterogeneity among subjects for transcriptomic, genetic and epigenetic analyses. We accomplish heterogeneity reduction either by using diagnostically discordant monozygotic twins and siblings in our studies or by dividing the ASD population into more homogeneous subgroups based on similar symptomatic profiles. The latter technique has proven to be especially useful in identifying subtype-dependent gene expression differences among groups of unrelated individuals with ASD relative to controls as well as subtype-dependent genetic variants (SNPs) and linkage loci. In both expression and genetic analyses, a number of shared genes/SNPs were also identified, demonstrating some of the expected biological commonality among the ASD subtypes. Interestingly, the shared SNPs exhibited distinctly different odds ratios in the different subtypes, demonstrating that the subtypes are genetically distinct in relation to these SNPs. Thus, a systems approach to ASD using integrative genomics coupled with phenotyping of subjects has led to the discovery of novel candidate genes relevant to pathobiological processes involved in ASD as well as to the identification of potential diagnostic biomarkers at multiple levels: gene expression, microRNA, DNA methylation, and genetics. One of the novel genes identified through our studies is retinoic acid-related orphan receptor alpha (*RORA*) which is a nuclear hormone receptor that not only regulates many other genes that are implicated in the pathobiology of ASD, but also is oppositely regulated by male and female hormones in a manner that suggests its contribution to the male bias in ASD. Ongoing studies are continuing to examine mechanisms of pathogenesis involving dysregulation of *RORA* as well as gene-environment interactions that elevate risk for ASD.

For more on Dr. Hu's Autism research, watch the video.

Publications

View publications *by this faculty member from January 1, 2013 - present*

Olivia Veatch, PhD
Scientist CAB Member

- My research focuses on uniting molecular and computational genetics to inform translational medicine for neuropsychiatric conditions.
- I combine cutting edge computational techniques for gene discovery and characterization, with the functional follow-up studies necessary for translation of genetic findings to humans.
- Much of my work has focused on repurposing data to help overcome challenges complicating identification and characterization of genes involved in autism.
- I use novel statistical methods to analyze previously collected phenotype data stored in large autism databases.
- Through this approach I have successfully identified symptom profiles in individuals with autism that are genetically-meaningful. I also re-analyze previously generated genetic data stored in large autism databases by applying approaches that evaluate how multiple genes acting together contribute to autism.

Dr. Veatch-Research Projects

- To better understand how genetic information can be useful to inform treatments for individuals with autism, I study how genetic factors contribute to presentation of common co-occurring medical conditions.
- I am especially interested in sleep and its effects on neurodevelopment. Sleep disturbances, particularly insomnia, are very common in individuals with autism.
- Interestingly, the known biological functions for many autism candidate genes suggest the involvement of shared biological pathways with sleep regulation.
- For example, defects in synaptic pruning during neurodevelopment disrupt the balance of synapses. Evidence indicates that abnormal synaptic pruning underlies the atypical neurodevelopment observed in many individuals with autism.

Dr. Veatch-Research Projects (Cont.)

- Sleep is also critical for synaptic homeostasis, with restricted sleep affecting synaptic pruning. Since sleep problems are common in autism, it is intriguing to consider the possibility of a connection where sleep problems worsen atypical synaptic pruning and lead to more severe issues in neurodevelopment.

- Identifying the genes that contribute to abnormal synaptic pruning during development will help us understand the causes and consequences of insomnia in individuals with autism.

Dr. Veatch-Research Projects (Cont.)

- The melatonin pathway is also particularly interesting because changes in the production of melatonin alter sleep patterns and are also implicated in autism. There are numerous genes that function to generate melatonin that are also candidate genes for autism.

- I am working on identifying and characterizing the specific genes affecting proper function of the melatonin pathway that also contribute to autism. This offers opportunities to discover more effective methods of treatment for sleep problems in individuals with autism, who have abnormalities in melatonin pathway genes.

- More information on my autism studies can be found at: http://www.ncbi.nlm.nih.gov/pubmed/?term=Veatch+O

Project Website-Update

- The project website has been updated, including addition of the "Patient Stories" section and agendas for the remaining presentations (under Methods tab).
- Please visit the website for more information. http://genetics-outcomes.net/EAIN

Methods

Develop Partnerships [Community Advisory Board (CAB) Formation]. Using the principles of community engaged research; our project team will develop and formalize relationships with twenty two stakeholders who will be engaged in every aspects of the project development process. These stakeholders will comprise the members of a formalized genetic concept Community Advisory Board (CAB). Seven of the CAB members have already been recruited by the research team members and engaged from the inception of the project through the application preparation and submission. Additional fifteen CAB members have been recruited at the beginning of the project by the research team members.

Members of the Research Team

Members of the Community Advisory Board-CAB

CAB Meetings. The CAB will convene six meetings at Children's Mercy Hospital or other locations suggested by the stakeholders during the twelve month project period and will work closely with the research team to develop the strategic direction of this engagement/ educational program. CAB members will be strongly encouraged to attend a minimum of 80% of all meetings in person, by telephone or video conference. The specific tasks and activities of each meeting are described below:

Meeting's Agenda (Tentative)

Meeting 1 (click for agenda)

Meeting 2 (click for agenda)

Meeting 3 (click for agenda)

Meeting 4 (click for agenda)

Meeting 5 (click for agenda)

Meeting 6 (click for agenda)

Patient Stories

In this section a number of our patient/parent representatives share their personal stories and why they are interested in genetic information. Some stories have more details to help us grasp the level of health complexity that some patients are dealing with, a long journey they have gone through to find an answer, and how they expect genetic information to help them with better managing health outcomes.

Please note that our Engagement project is not focused on any specific disease. We would be happy to add more patient stories, please feel free to send us your story!

Patient Story 1: Seth Bittker
Patient story 2: Kristen Worden
Patient Story 3: DeeJo Miller
Patient Story 4: Sheryl Chadwick
Patient story 5: Mary Anne Hammond

The following videos provide more information on Precision Medicine Initiative and patient stories.

Personal Genomics: Use of personal genomics in predictive and precision medicine
https://www.youtube.com/watch?v=pSzk-yf6BVU (length: 54 min)

What Is Next? Collecting Participants' Feedback!

- **Survey:** PPT#3 evaluation survey will be sent out to get an overall assessment from all participants about this presentation. It will include questions to evaluate the content. Please respond to the survey at your earliest convenience.

- All collected feedback, comments, questions and responses will be summarized and posted on the project website
  - (http://genetics-outcomes.net/EAIN/) and
  - shared in our next presentation (PPT #4).