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

PCORI-EAIN 2419 Presentation #2

Principle Investigator:
Zohreh Talebizadeh, PhD

Outline

- 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? Collecting participants' feedback!

Introduction

- In the PPT#1, we described CER, PCOR, and the overall goals of this engagement project.
- 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:
  - The results of the PPT#1 evaluation survey will be shared.
  - We will briefly review the concepts of genetics and Precision Medicine Initiative.
  - Our patient/parent stakeholders will share their stories.

PPT#1 Evaluation Survey-Results

All members responded (N=33)

For the following two statements, please indicate to what extent you disagree or agree with "0" indicating "Strongly disagree" and "10" indicating "Strongly agree".	Rating Average	Response Count
1) The information in the **Meeting#1 presentation** was provided in an easy to understand manner.	**8.82**	33
2) The information in the **Project's website** was provided in an easy to understand manner.	**8.79**	33
answered question	**33**	**33**

2. I agree with the information described in the project's Memorandum of Agreement (MOA).

Answer Options	Response %	Response Count
Yes, I agree	**100.0%**	33
No, I do not agree	0.0%	0
answered question		**33**

3. I agree with the suggested structure for the meetings.

Answer Options	Response %	Response Count
Yes, I agree	**100.0%**	33
No, I do not agree	0.0%	0
answered question		**33**

4. I agree with the selection of topics to be covered during the course of this project.

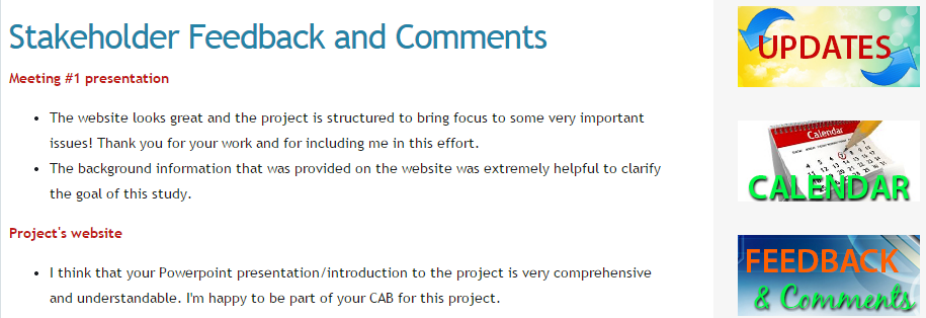
Answer Options	Response %	Response Count
Yes, I agree	**100.0%**	33
No, I do not agree	0.0%	0
answered question		**33**

5. I would like to have a personal meeting and/or call with the PI for further clarification of materials discussed in the Meeting#1 presentation?

Answer Options	Response %	Response Count
Yes, I would like to have a meeting/call for further clarification	**6.1%**	2
Not at this point	**93.9%**	31
answered question		**33**

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)
  - 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#1 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#1 group discussion was held on 3/3/2016, meeting notes will be posted on the website.

PPT#1
group discussion

PCORI Feedback

- The PI (Zohreh) and Kelly Ranallo, our CAB community leader and parent representative, visited PCORI on 3/24/2016 to provide update on the EAIN-2419 project and get their feedback. The Engagement team was pleased with our overall progress and the project website.
- Thanks to all of you for making this project possible!
- Special thanks to Kelly for joining me and sharing her perspectives, as a representative of our CAB, with the PCORI staff during this visit.

Genetics

- NIH created an easy to understand booklet for public education about the concept of genetics. It is a great resource explaining this topic and we decided to use it to provide an overview of genetics for our study participants. The document is called **From the Blueprint to You** and here are the links to each chapter, for your review:
  - From the Blueprint to You: A Brief Guide to Genetics
  - DNA as the Instruction Book
  - The Genetic Code: Figure A
  - Making a Protein: Figure B
  - Human Genome Project
  - Implications for the Future
  - Glossary of Terms

Precision Medicine Initiative (PMI)

- President Obama announced a $215 million investment in the President's 2016 Budget to support PMI and advance toward a new era of individualized treatment (**Source:** *White House Press Office*)
  - "I want the country that eliminated polio and mapped the human genome to lead a new era of medicine—one that delivers the right treatment at the right time...Tonight, I'm launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes—and to give all of us access to the personalized information we need to keep ourselves and our families healthier." —*President Barack Obama, State of the Union Address, January 20, 2015*

PMI (Cont.)

More details about the concept and overall goal of this initiative can be found here:

- What is Precision Medicine?
  - https://www.youtube.com/watch?v=HQKFgfMO5Sw (length: 1:50 min)
- Precision Medicine 2016: A Virtual Conference
  - https://www.youtube.com/watch?v=pUt_RF3Ky4A (length: 3 min)
- The Precision Medicine Initiative Website
  - https://www.whitehouse.gov/precision-medicine

Patient/Parent Stories

- In this section a number of our patient/parent representatives share their personal stories and why they are interested in genetic information.
- The first story (by Seth Bittker) has 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 in our future presentations, please feel free to send us your story!

Patient Story 1: Portrait of my family (Seth Bittker)

- **Me** (46 years old): Pains in extremities, insomnia, and digestive issues. Onset gradual but got bad about four years ago
- **My son** (9 years old): Autism diagnosis when younger, regressive but likes bonding, great memory, slow processing, very bad handwriting
- **My daughter** (7 years old): Modest OCD
- **Sister** (44 years old): Arthritis, nerve degeneration, insomnia, and fatigue. Was using a wheelchair briefly but somewhat better now. Onset about 11 years ago after birth of first child
- **Mother** (73 years old): Arthritis like condition, bones break easily, pains in joints
- **Father** (76 years old): Healthy

Can genetic information provide some insight into what is affecting my family?

Alternative Treatments

- My mother, my sister, me, my son, and my daughter have all been through incidents where we were negatively affected by oral supplementation of vitamin D.
- Very high levels of oxidative stress in the family based on test results. I need antioxidants to fall asleep. My son also does well on a carotenoid mix.
- It seems that something like celiac affects my family.
- Some supplements are helpful:
  - Me, my sister, my mother, and my daughter but not my son benefit from carnitine supplementation.
  - Me, my sister, and my mother seem to benefit from thiamine.
  - All of us seem to benefit from methylfolate.
  - My son needs supplemental methylcobalamin. He has modest methylmalonic acidemia based on test results. Without methylcobalamin he will regress.
  - My sister and mother and to a lesser extent myself benefit from lysine.
- Some signs in test results of auto-immunity, but traditional rheumatological medicines and analgesics were not helpful.

Genetic Tests

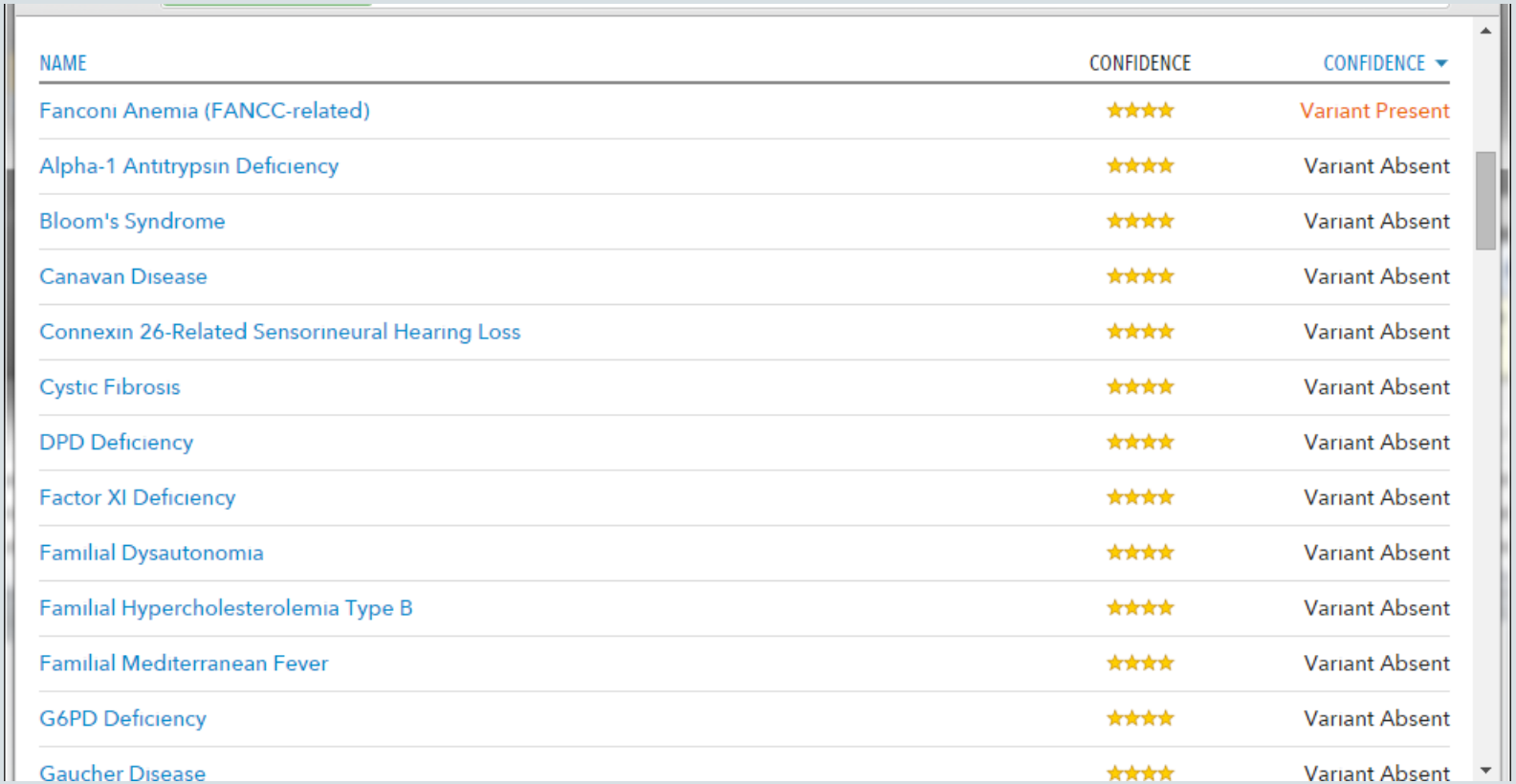
- We have done a number of clinical genetic testing with no definite diagnosis, but some suggestive evidences.
  - My sister and my mother have a defect on mitochondrial DNA (mtDNA) of unknown significance. Since mtDNA is inherited solely from the mother, I would have it too. Therefore, it may be a contributor, but may not be the primary causative issue with respect to our family health conditions. Because my mtDNA would not be passed onto my kids and I see some aspects of what affects me and affects them as similar.
  - We did different genome tests (i.e., genes related to neurology and autism for me and my son, respectively, and whole genome test for my sister and parents)
  - The test did reveal that I have two gene defects associated with Charcot-Marie-Tooth disease but I have one of each gene and supposedly you need two bad copies to show the symptoms.
  - I also decided to use direct to consumer genetic service, hoping to find an answer for our complex family health conditions.

What is Direct-to-Consumer (DTC) genetic testing?

- It provides genetic reports directly to consumers (no need to get health care provider referrals).
- One of these DTC companies is called 23andMe and I used their services.
- In addition to a limited FDA approved genetic risk factor reports, raw genetic data is also provided to consumers.
- It is based on saliva samples and we were not able to get enough sample from my son but did the testing on me and my sister.

EXAMPLE:

23andMe–Inherited Conditions

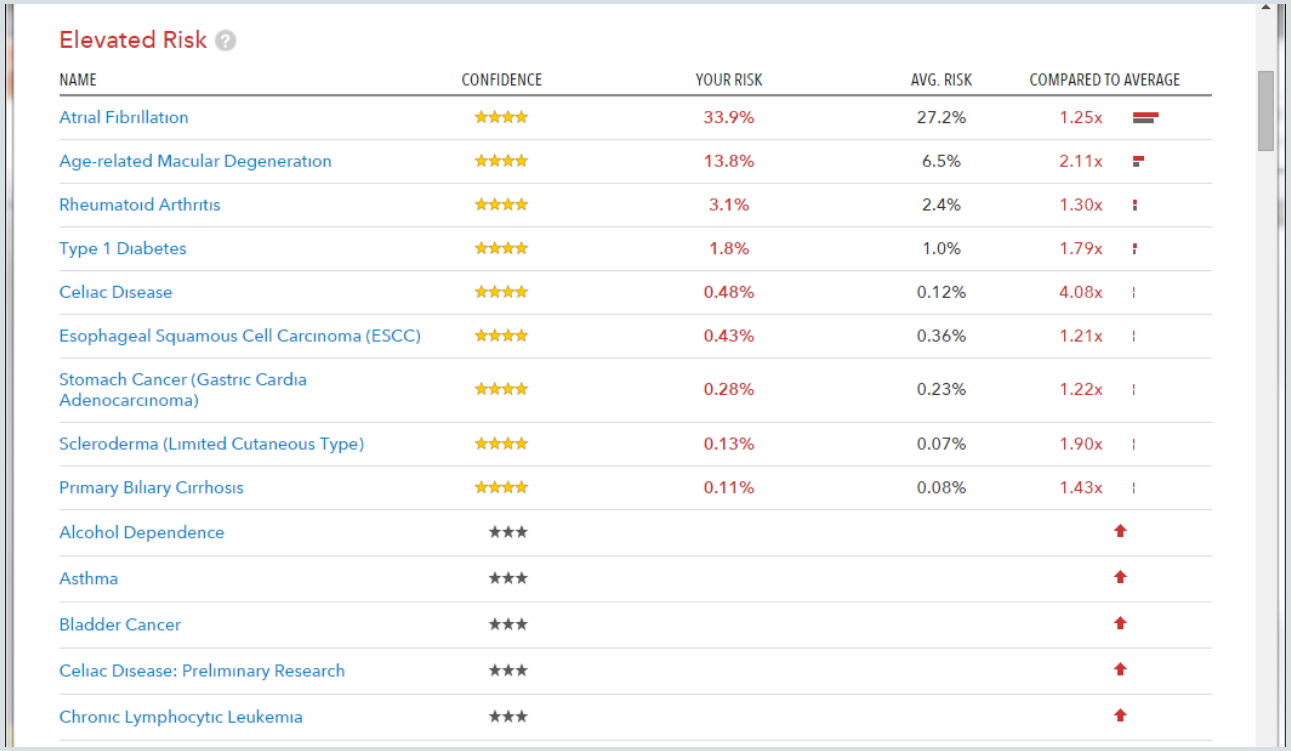


NAME	CONFIDENCE	CONFIDENCE
Fanconi Anemia (FANCC-related)	★★★★	Variant Present
Alpha-1 Antitrypsin Deficiency	★★★★	Variant Absent
Bloom's Syndrome	★★★★	Variant Absent
Canavan Disease	★★★★	Variant Absent
Connexin 26-Related Sensorineural Hearing Loss	★★★★	Variant Absent
Cystic Fibrosis	★★★★	Variant Absent
DPD Deficiency	★★★★	Variant Absent
Factor XI Deficiency	★★★★	Variant Absent
Familial Dysautonomia	★★★★	Variant Absent
Familial Hypercholesterolemia Type B	★★★★	Variant Absent
Familial Mediterranean Fever	★★★★	Variant Absent
G6PD Deficiency	★★★★	Variant Absent
Gaucher Disease	★★★★	Variant Absent

Typically, it is available for known recessive genetic conditions (requires 2 copies of mutations). The report shows if consumer has one of the known mutations.

EXAMPLE:

23andMe–Health Reports



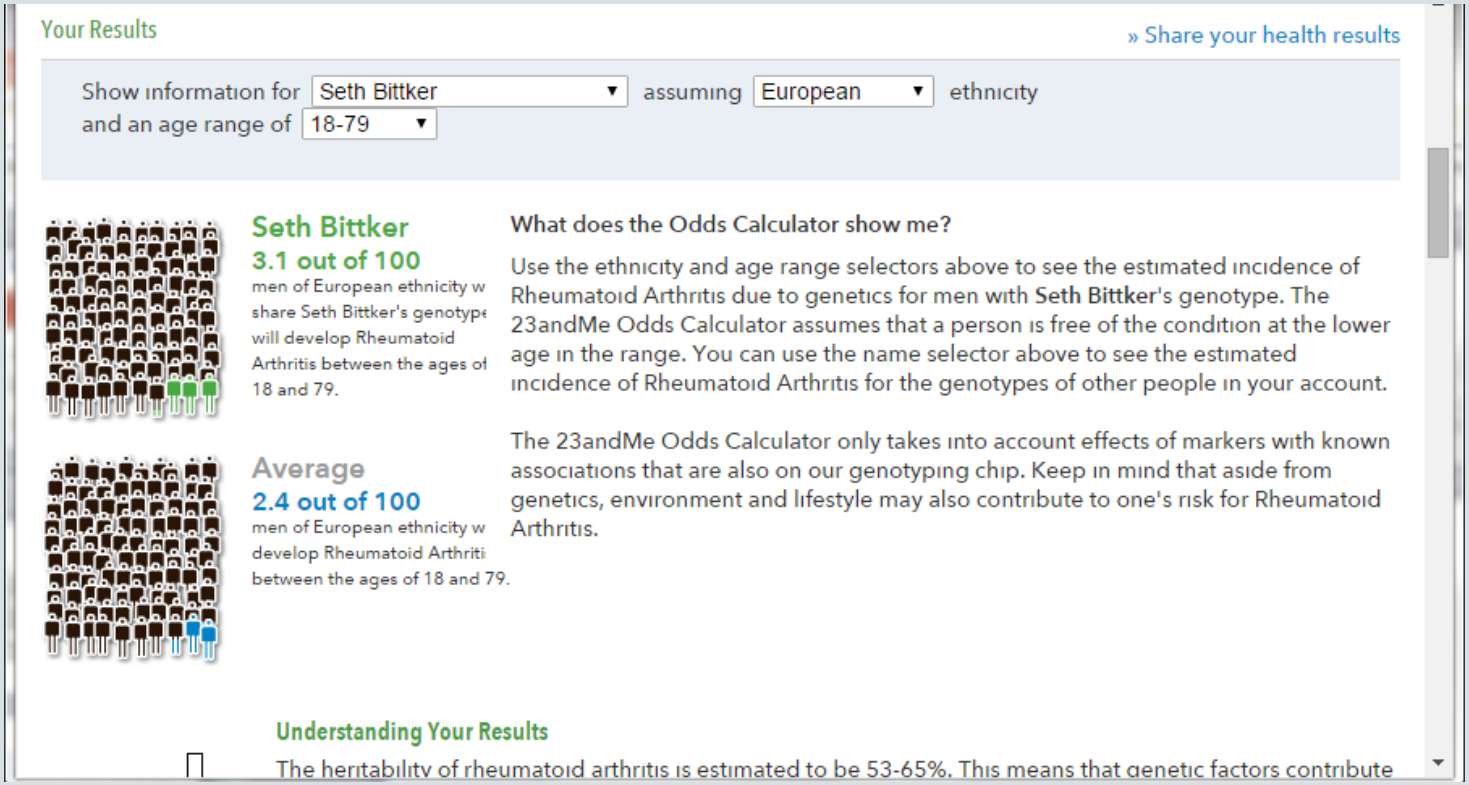
Elevated Risk

NAME	CONFIDENCE	YOUR RISK	AVG. RISK	COMPARED TO AVERAGE
Atrial Fibrillation	★★★★	33.9%	27.2%	1.25x
Age-related Macular Degeneration	★★★★	13.8%	6.5%	2.11x
Rheumatoid Arthritis	★★★★	3.1%	2.4%	1.30x
Type 1 Diabetes	★★★★	1.8%	1.0%	1.79x
Celiac Disease	★★★★	0.48%	0.12%	4.08x
Esophageal Squamous Cell Carcinoma (ESCC)	★★★★	0.43%	0.36%	1.21x
Stomach Cancer (Gastric Cardia Adenocarcinoma)	★★★★	0.28%	0.23%	1.22x
Scleroderma (Limited Cutaneous Type)	★★★★	0.13%	0.07%	1.90x
Primary Biliary Cirrhosis	★★★★	0.11%	0.08%	1.43x
Alcohol Dependence	★★★			
Asthma	★★★			
Bladder Cancer	★★★			
Celiac Disease: Preliminary Research	★★★			
Chronic Lymphocytic Leukemia	★★★			

Health reports provide risk prediction summary of conditions for which consumer is at increased or decreased risk.

EXAMPLE:

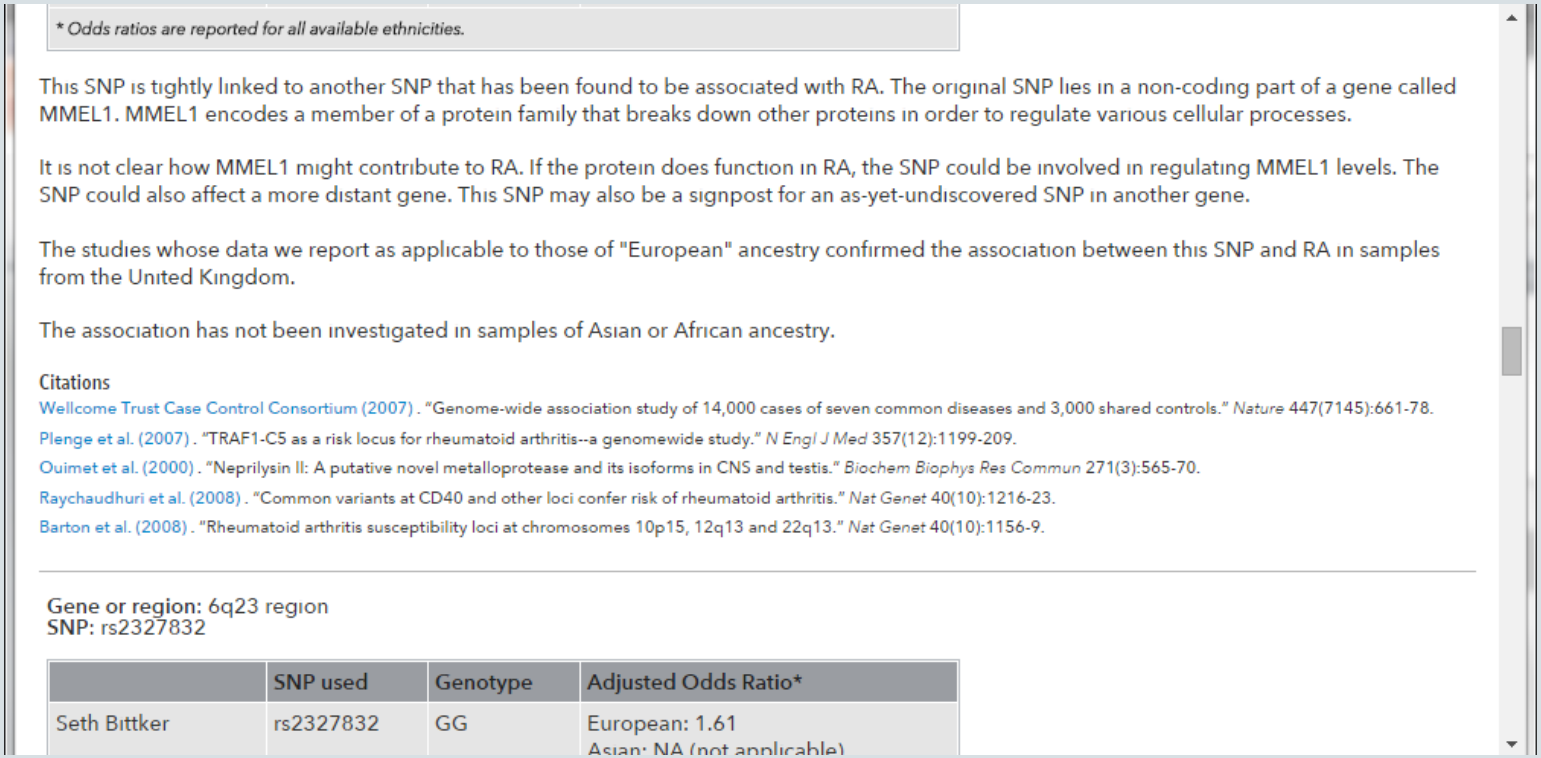
23andMe–Disease Overview



It provides more details about the meaning of calculated risks for diseases and could be useful for educated non-specialist.

EXAMPLE:

23andMe–Technical Reports



** Odds ratios are reported for all available ethnicities.*

This SNP is tightly linked to another SNP that has been found to be associated with RA. The original SNP lies in a non-coding part of a gene called MMEL1. MMEL1 encodes a member of a protein family that breaks down other proteins in order to regulate various cellular processes.

It is not clear how MMEL1 might contribute to RA. If the protein does function in RA, the SNP could be involved in regulating MMEL1 levels. The SNP could also affect a more distant gene. This SNP may also be a signpost for an as-yet-undiscovered SNP in another gene.

The studies whose data we report as applicable to those of "European" ancestry confirmed the association between this SNP and RA in samples from the United Kingdom.

The association has not been investigated in samples of Asian or African ancestry.

Citations

Wellcome Trust Case Control Consortium (2007) . "Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls." *Nature* 447(7145):661-78.

Plenge et al. (2007) . "TRAF1-C5 as a risk locus for rheumatoid arthritis--a genomewide study." *N Engl J Med* 357(12):1199-209.

Ouimet et al. (2000) . "Neprilysin II: A putative novel metalloprotease and its isoforms in CNS and testis." *Biochem Biophys Res Commun* 271(3):565-70.

Raychaudhuri et al. (2008) . "Common variants at CD40 and other loci confer risk of rheumatoid arthritis." *Nat Genet* 40(10):1216-23.

Barton et al. (2008) . "Rheumatoid arthritis susceptibility loci at chromosomes 10p15, 12q13 and 22q13." *Nat Genet* 40(10):1156-9.

Gene or region: 6q23 region
SNP: rs2327832

	SNP used	Genotype	Adjusted Odds Ratio*
Seth Bittker	rs2327832	GG	European: 1.61 Asian: NA (not applicable)

Technical reports provide more technical detail for genetic risk factors (SNPs). For example, it shows SNP level contribution to odds ratio and related references (scientific literatures).

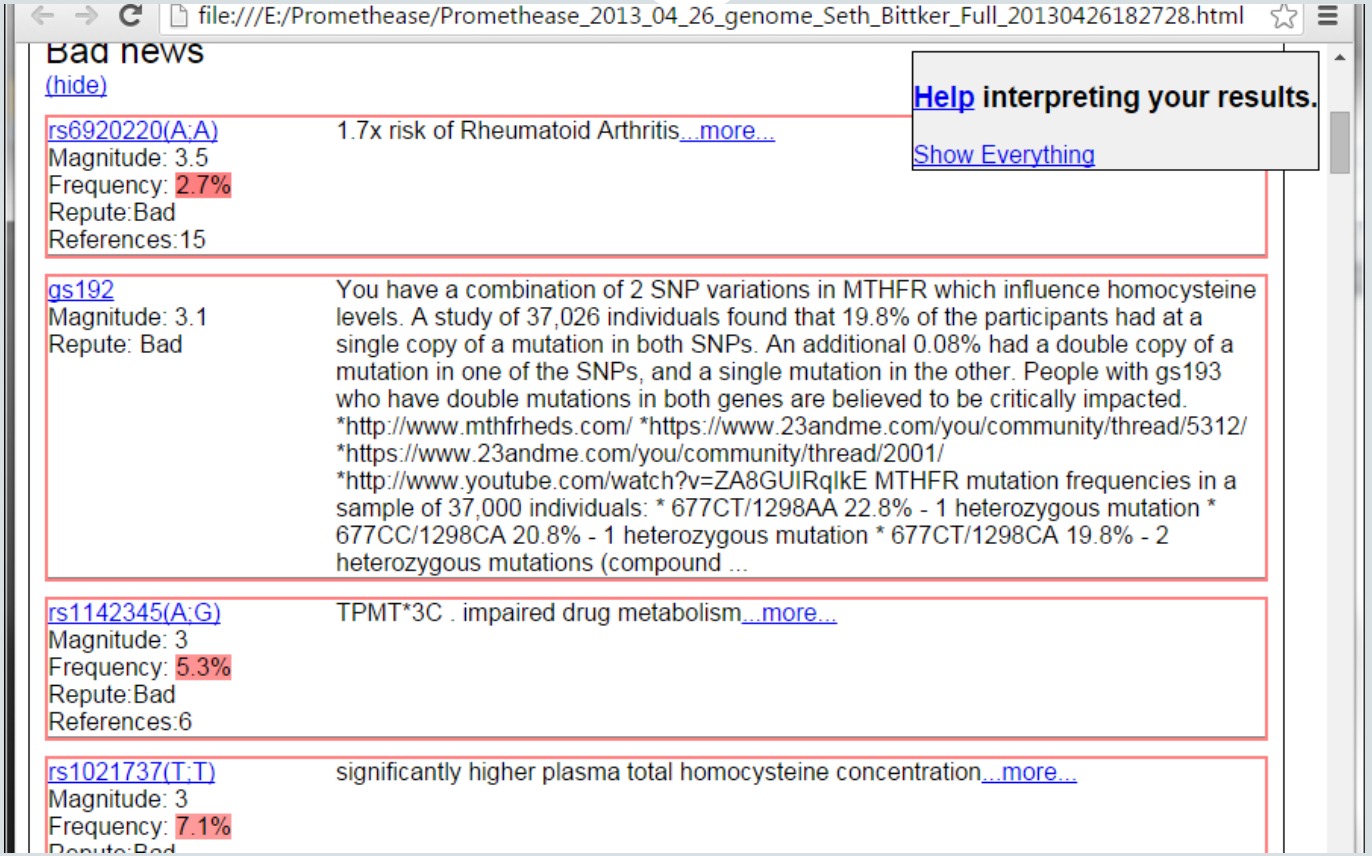
23andMe–Raw Data

- 23andMe offers a service to allow users download raw data (not analyzed genetic data).

- Raw data can be then analyzed using other resources or tools. For example:
  - Promethease
  - SNPedia

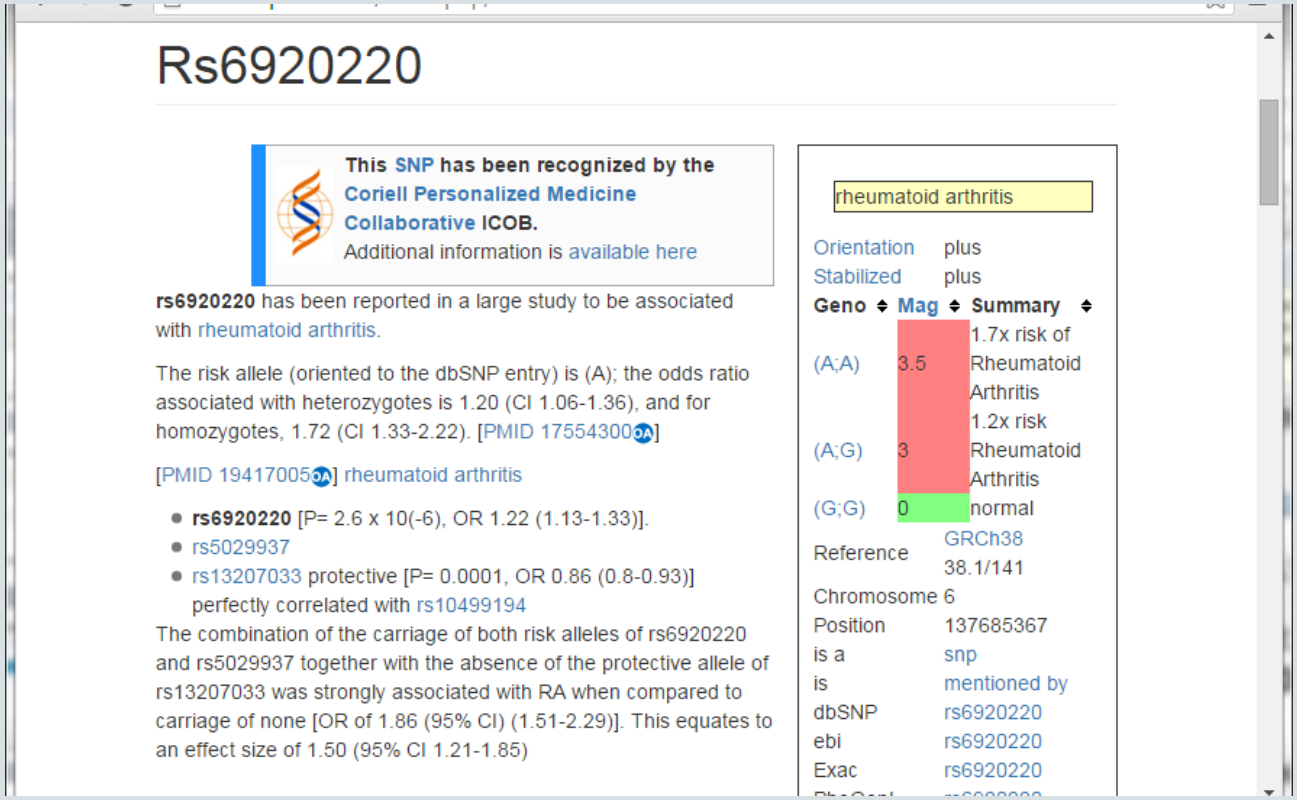
- I used these two tools to interpret my own 23andMe raw genetic data (Example: next two slides).

EXAMPLE: Promethease



Promethease provides more detailed reports than 23andMe but less understandable for lay consumers.

EXAMPLE: SNPedia



Rs6920220

This SNP has been recognized by the Coriell Personalized Medicine Collaborative ICOB.
Additional information is available here

rs6920220 has been reported in a large study to be associated with rheumatoid arthritis.

The risk allele (oriented to the dbSNP entry) is (A); the odds ratio associated with heterozygotes is 1.20 (CI 1.06-1.36), and for homozygotes, 1.72 (CI 1.33-2.22). [PMID 17554300]

[PMID 19417005] rheumatoid arthritis

- **rs6920220** [P= 2.6 x 10(-6), OR 1.22 (1.13-1.33)].
- rs5029937
- rs13207033 protective [P= 0.0001, OR 0.86 (0.8-0.93)] perfectly correlated with rs10499194

The combination of the carriage of both risk alleles of rs6920220 and rs5029937 together with the absence of the protective allele of rs13207033 was strongly associated with RA when compared to carriage of none [OR of 1.86 (95% CI) (1.51-2.29)]. This equates to an effect size of 1.50 (95% CI 1.21-1.85)

rheumatoid arthritis

Orientation		plus
Stabilized		plus
Geno	**Mag**	**Summary**
(A;A)	3.5	1.7x risk of Rheumatoid Arthritis
(A;G)	3	1.2x risk Rheumatoid Arthritis
(G;G)	0	normal
Reference		GRCh38 38.1/141
Chromosome		6
Position		137685367
is a		snp
is		mentioned by
dbSNP		rs6920220
ebi		rs6920220
Exac		rs6920220

SNPedia provides detailed information about SNPs and what the risks for particular polymorphisms are.

What I learned from using DTC genetic testing?

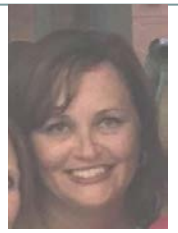
- I was hoping to find information that would help me better understand:
  - Which genetic polymorphisms are critical in the dysfunction that seems to be affecting my family?
  - Can we identify treatment options based on genetic information?

- However, I learned that:
  - There are no reliable resources to help patients answer these type of health related questions.
  - Using DTC resources was interesting but did not fulfill my needs.
  - There is a tremendous complexity in understanding genetic information.
  - Most likely, genetic data needs to be evaluated in relation with other biochemical testing.
  - It requires integrating genetic data into making diagnosis and selecting treatments, but currently there is no established method for health care providers and patients to do so.

Why am I interested to contribute to the EAIN-2419 project?

- After reading a large number of publications and educating myself about research on genetics of various conditions, I was disappointed to see that, despite many findings, the research community has not yet found practical ways to use published knowledge to improve patients' health.
- This PCORI project provides an excellent opportunity for the exchange of knowledge and expectations between patients/parents like me and the clinical and scientific experts, so our voices and opinions will be heard.
- As a parent eager to understand the biology and treatments of ASD, I have recently launched an in-depth interview series that I call Autism Research Connections. The focus is on translational research on autism biochemistry and therapeutics.

Patient Story 2: (Kristen Worden)



- I am a breast cancer survivor. I also have worked in the pharmaceutical research industry for over 15 years. I would like to share with you my experience as a patient and professional observations.
- I tested positive for the BRCA1 genetic mutation. Once the location of the mutation was identified, my father was tested and he was positive as well. I also have 1 sister that was positive. After genetic counseling, we learned of our chances for certain other cancers. Mine were higher since I had breast cancer. With this information, my sister decided to have a prophylactic double mastectomy (after I had mine) and then a total hysterectomy (after mine) to eliminate her risk of getting cancer. This was 8 years ago, so still a drastic decision - however, thankfully we had doctors that understood the risk and genetics behind it and allowed us to make the decisions that were best for us. I remember when they called me to tell me that I had the mutation - they asked if I was sitting down. Honestly, I was happy to hear I had it. I got a rare look into what 'could be' in store for me health-wise. It allowed me to make decisions proactively that most people don't get the opportunity to make. I am screened for skin cancer, colonoscopies are done sooner than would be normally. I now feel in control of things that I would not get to be otherwise.

Patient Story 2 (Cont.)

- Working in the pharmaceutical research industry for over 15 years has really allowed me to understand how many pieces go into getting a drug to market. For example, I worked on an osteoporosis study where a large number of the patient populations were breast cancer survivors. It was determined during the study that some of those survivors were seeing positive effects from the study drug toward their tumors. These findings caused the pharma company to re-develop the protocol with the new indication for breast cancer treatment.

- A lot of the studies I work on also utilize patient diaries for the data that captured. This piece is very important as personal experiences are equally as important as the science behind the drugs. This information is vital to understanding any adverse affects of the medications as well as just understanding the patient's feelings and how the drug affects their daily activities and functions.

Patient Story 3: (DeeJo Miller)

- My daughter was diagnosed with cancer when she was 13 years old. She went from being a Junior Olympic gold medal weightlifter in August of 2004 to being diagnosed with stage IV Burkitt's Lymphoma in September of 2004. After ten rounds of intense chemotherapy it seemed her treatment phase was complete. Unfortunately, only eight weeks later, we found out her cancer was back.
- Further testing showed she had a chromosomal translocation. Was there a reason that her body didn't react to the initial treatment in the 'typical' way? We were left with very few options and they all seemed to be a shot in the dark.
- We chose to pursue very aggressive treatment. She contracted a deadly fungal infection and endured multiple surgeries. After being dropped from the clinical trial she was enrolled in, she needed a bone marrow transplant. Through even more obstacles she received an autologus stem cell transplant in November 2005.

Patient Story 3 (Cont.)

- As a parent making such life and death decisions with only 'hope' as our guide, I was often distressed wondering if we were subjecting my daughter to treatments that because of her genetic make-up, were futile. In the end, she survived. She has permanent medical side effects as a result of her treatment that will require her to receive IgG infusions for the rest of her life. At this time, her infusions cost over $8,000 per month. Was there another treatment option available that would not have been so life-altering?
- I have been an advocate for the American Cancer Society and the Leukemia and Lymphoma Society for many years. I have been on staff, representing the voice of parents, at Children's Mercy since 2008. Working at Children's Mercy I have met many other parents who struggle with finding a treatment for their children. I am excited about the possibilities of improving patients' health and outcomes through the use of genetic knowledge that has already been gathered.
- I am hopeful that this novel, and structured engagement activity may facilitate providing others with information that wasn't available for my daughter and her medical team.

Patient Story 4: (Sheryl Chadwick)

- My son was diagnosed with Acute Lymphoblastic Leukemia (ALL) at the age of six. His protocol included 3 ½ years of chemotherapy. During my son's induction phase, the goal was for him to go into remission (having less than 5% leukemia cells in his bone marrow) within 7 days.

- Unfortunately my son did not go into remission within the first week. He was tested again at 14 days, and he was still not in remission. My son finally went into remission at 28 days. Because it took so long for him to go into remission, his entire protocol was altered from a standard ALL treatment to a high risk augmented protocol which increased the chemotherapy dosages and frequencies for the entire 3 ½ years of treatment.

Patient Story 4 (Cont.)

- Throughout his treatment, he suffered from multiple side effects from having a suppressed immune system. He acquired invasive nasal fungus in two separate years that resulted in 17 nasal surgeries. The fungus also spread to his lungs and liver. He endured shingles many times as well as other viruses. He also experienced reflex sympathetic dystrophy.

- I have often wondered if there was a targeted treatment available that would have been designed specifically for him how much personal suffering could have been avoided.

- I hope that my son's difficult experience can contribute to initiatives that will help other children in the future that will be diagnosed with cancer. Additionally, I hope that patients and families will be given more education about the treatment choices that are available so they can make an informed decision about their health care.

Patient Story 5: (Mary Anne Hammond)

- I am the parent of a beautiful 22 year old daughter who has a heart defect, GI issues, a profound intellectual disability and severe autism spectrum disorder. Kailey is completely non-verbal and functions cognitively at about a 12 month old level. She depends on us for all of her daily living skills and is both a tremendous gift and a tremendous responsibility. She takes many medications to manage behavioral and health conditions. Balancing the side effects of numerous medications is a reality of most families who have loved ones with co-morbidities.
- Informed, understandable information is critical in families making good choices in regard to medications and treatments.
- As a parent, a community advocate and an education coordinator for Autism, I am excited that in this PCORI project we are working to look at genetic information to help predict patient outcomes. Hopefully, the knowledge gained will serve as power for those trying to make the best decision for treatment for their loved ones.

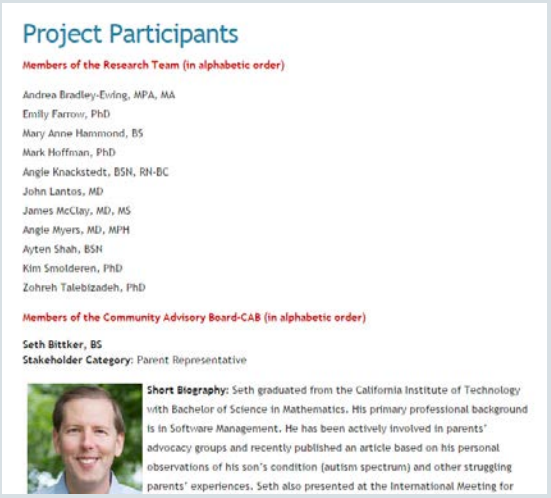
Additional Patient Stories & PMI

The following videos provide more information on PMI and patient stories:

- Personal Genomics: Use of personal genomics in predictive and precision medicine (length: 54 min)
  - https://www.youtube.com/watch?v=pSzk-yf6BVU
- Personalized Medicine: What Patients Have to Say to Industry (length: 27 min)
  - https://www.youtube.com/watch?v=Ss1o4sQt8Ko
- The White House Hosts a Precision Medicine Initiative Summit (length: 42 min)
  - https://www.youtube.com/watch?v=5dpwG8HpPgI

Update-Project Website

- The project website has been updated, including addition of short bios of all study participants, past and upcoming events, and feedback. Please visit the website for more information. http://genetics-outcomes.net/EAIN



Project Participants

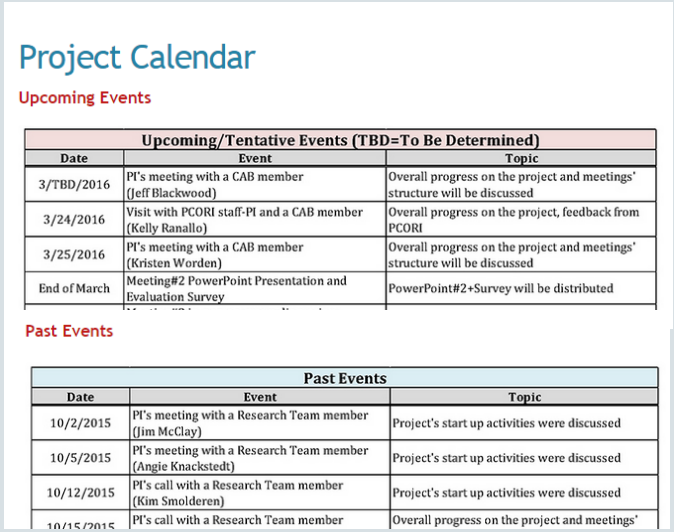
Members of the Research Team (in alphabetic order)

Andrea Bradley-Ewing, MPA, MA
Emily Farrow, PhD
Mary Anne Hammond, BS
Mark Hoffman, PhD
Angie Knackstedt, BSN, RN-BC
John Lantos, MD
James McClay, MD, MS
Angie Myers, MD, MPH
Ayten Shah, BSN
Kim Smolderen, PhD
Zohreh Talebizadeh, PhD

Members of the Community Advisory Board-CAB (in alphabetic order)

Seth Bittker, BS
Stakeholder Category: Parent Representative

Short Biography: Seth graduated from the California Institute of Technology with Bachelor of Science in Mathematics. His primary professional background is in Software Management. He has been actively involved in parents' advocacy groups and recently published an article based on his personal observations of his son's condition (autism spectrum) and other struggling parents' experiences. Seth also presented at the International Meeting for



Project Calendar

Upcoming Events

Upcoming/Tentative Events (TBD=To Be Determined)		
Date	**Event**	**Topic**
3/TBD/2016	PI's meeting with a CAB member (Jeff Blackwood)	Overall progress on the project and meetings' structure will be discussed
3/24/2016	Visit with PCORI staff-PI and a CAB member (Kelly Ranallo)	Overall progress on the project, feedback from PCORI
3/25/2016	PI's meeting with a CAB member (Kristen Worden)	Overall progress on the project and meetings' structure will be discussed
End of March	Meeting#2 PowerPoint Presentation and Evaluation Survey	PowerPoint#2+Survey will be distributed

Past Events

Past Events		
Date	**Event**	**Topic**
10/2/2015	PI's meeting with a Research Team member (Jim McClay)	Project's start up activities were discussed
10/5/2015	PI's meeting with a Research Team member (Angie Knackstedt)	Project's start up activities were discussed
10/12/2015	PI's call with a Research Team member (Kim Smolderen)	Project's start up activities were discussed
10/15/2015	PI's call with a Research Team member	Overall progress on the project and meetings'

Stakeholder Feedback and Comments

Meeting #1 presentation

- The website looks great and the project is structured to bring focus to some very important issues! Thank you for your work and for including me in this effort.
- The background information that was provided on the website was extremely helpful to clarify the goal of this study.

Project's website

- I think that your Powerpoint presentation/introduction to the project is very comprehensive and understandable. I'm happy to be part of your CAB for this project.

What is next? Collecting participants' feedback!

- **Survey:** PPT#2 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 #3).