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.

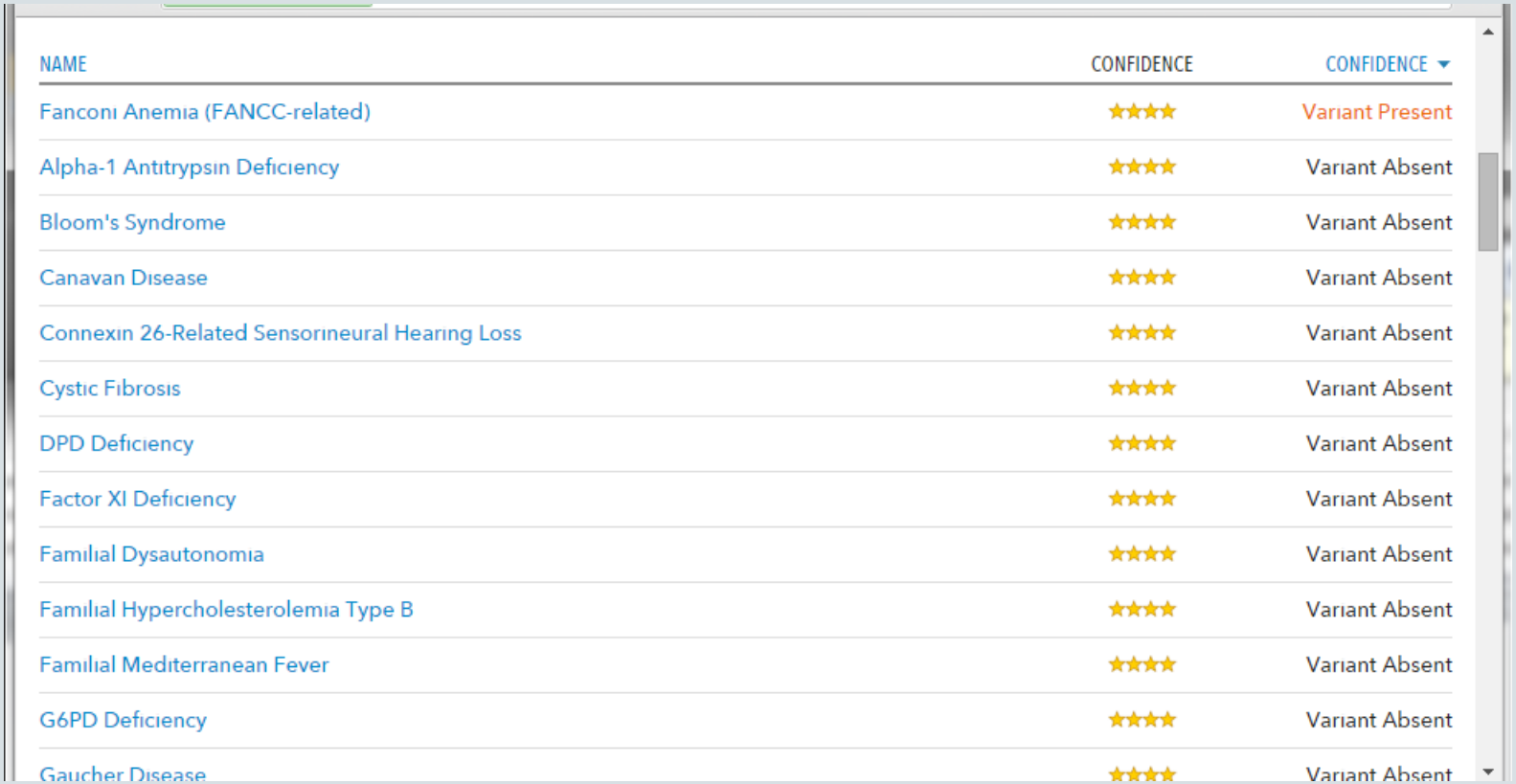
Genetic Tests

- 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.

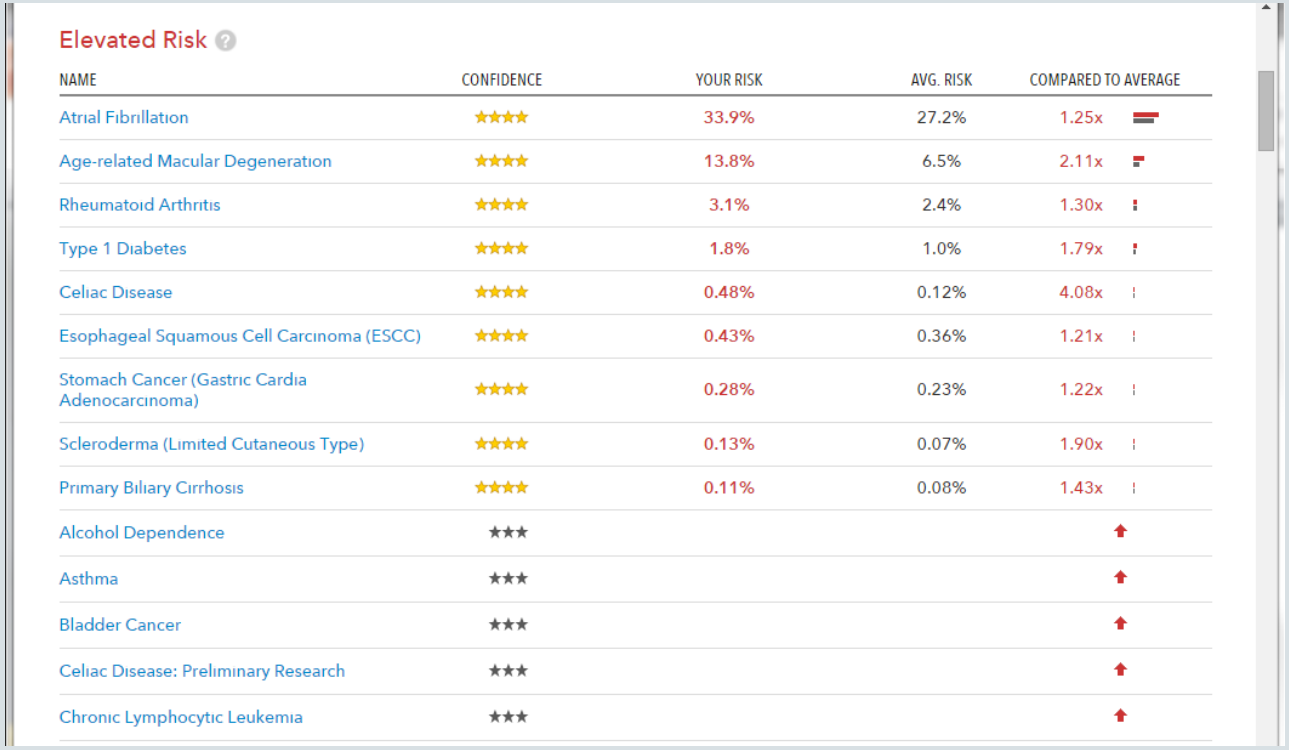
EXAMPLE:
23andMe–Inherited Conditions



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

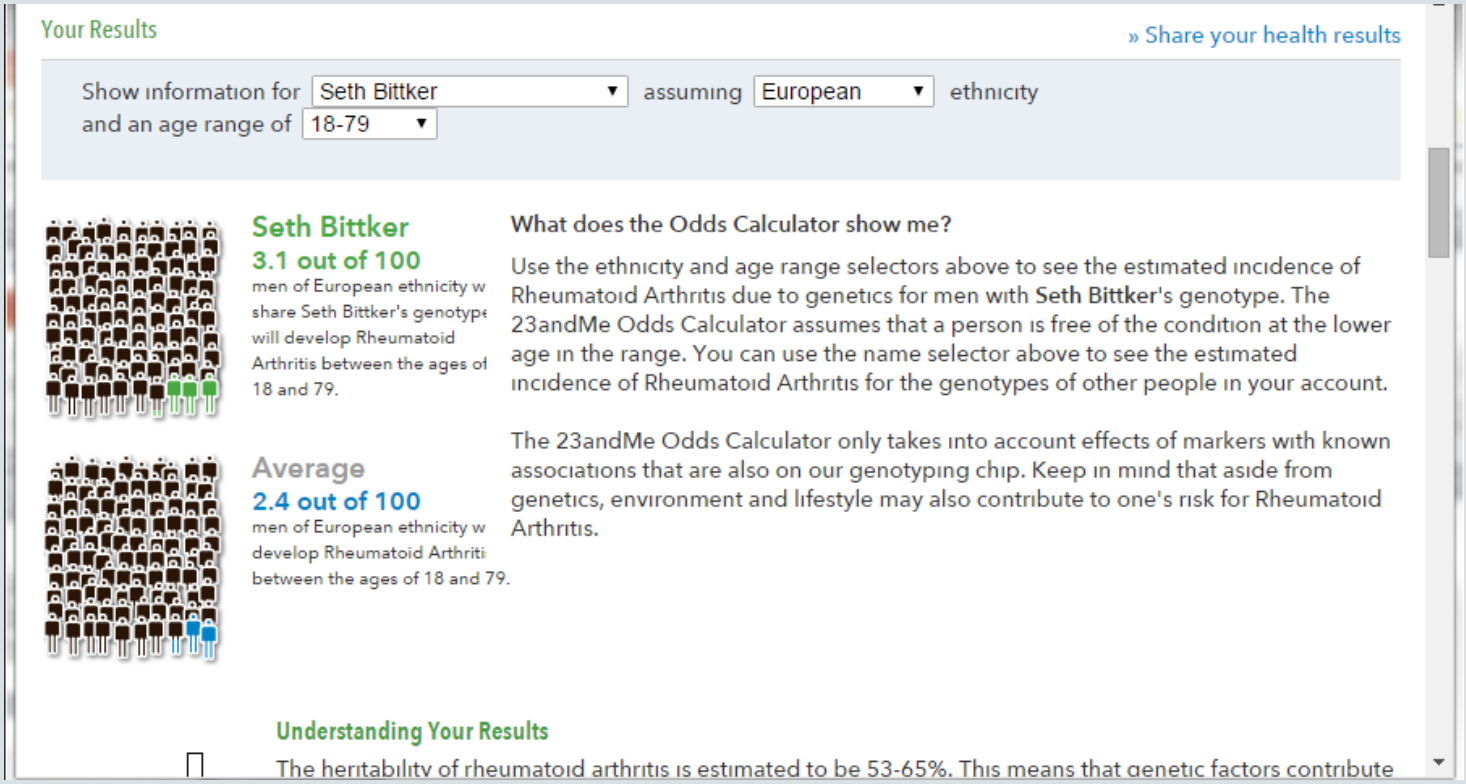


Elevated Risk

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	★★★			

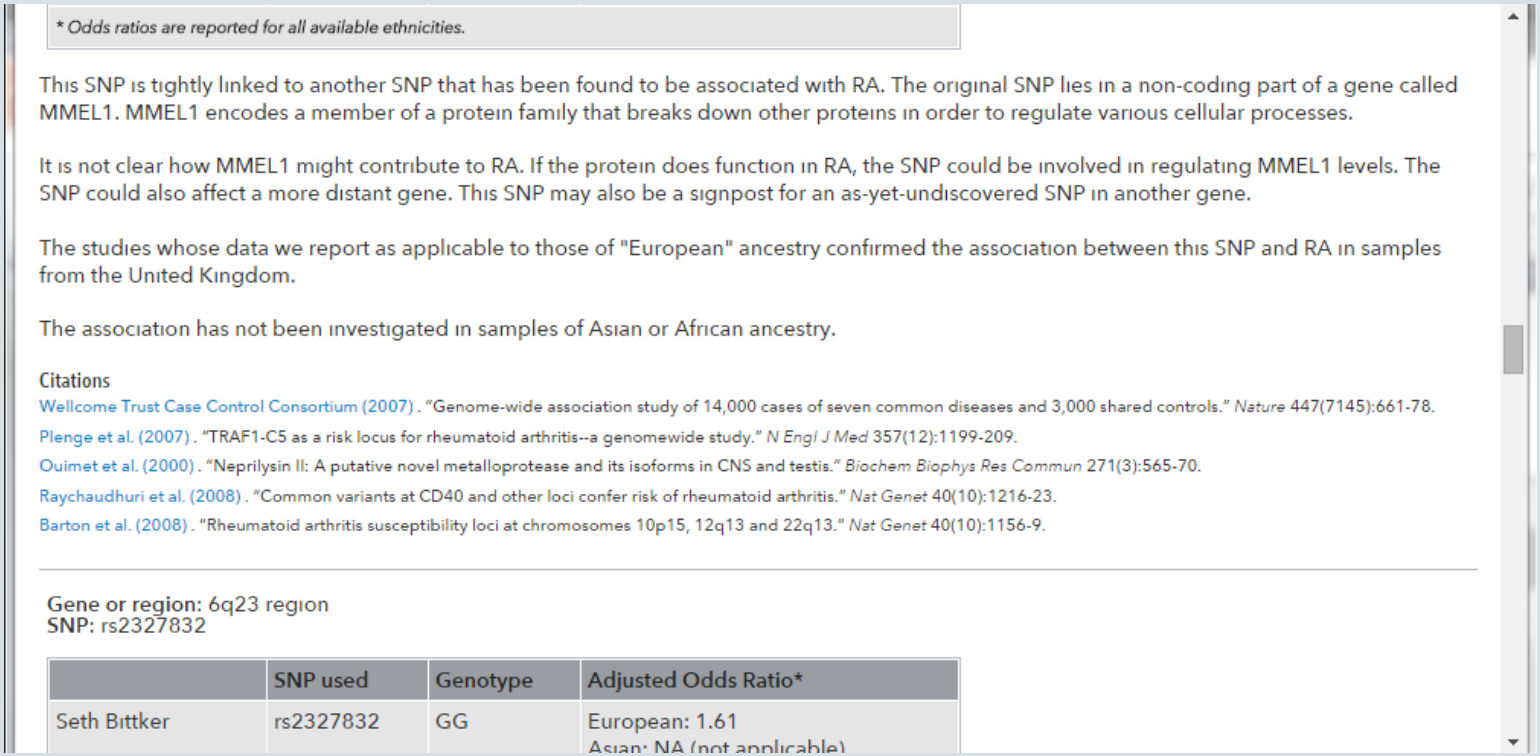
Health reports provide risk prediction summary of conditions for which consumer is at increased or decreased risk.

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).

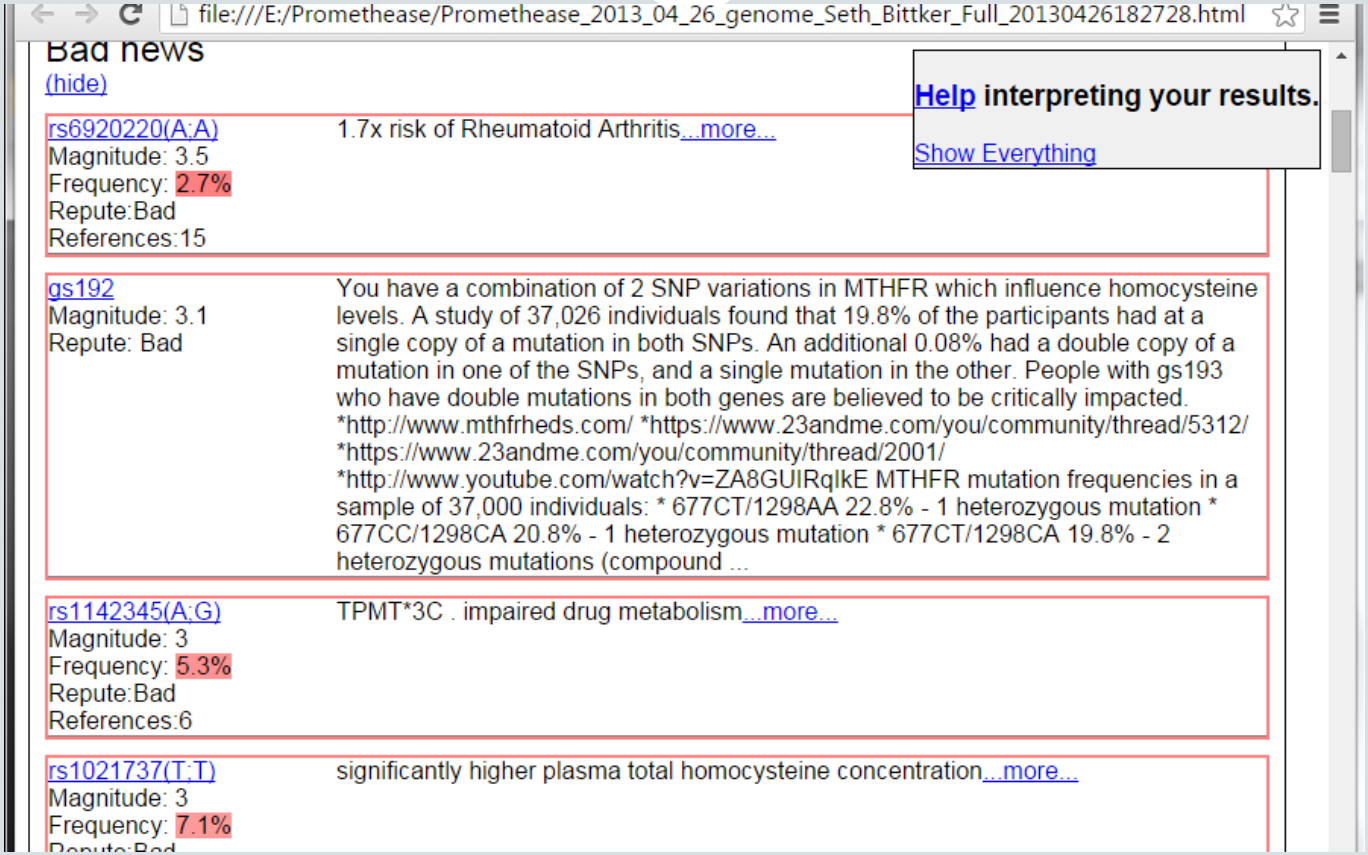
23andMe–Raw Data

- 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

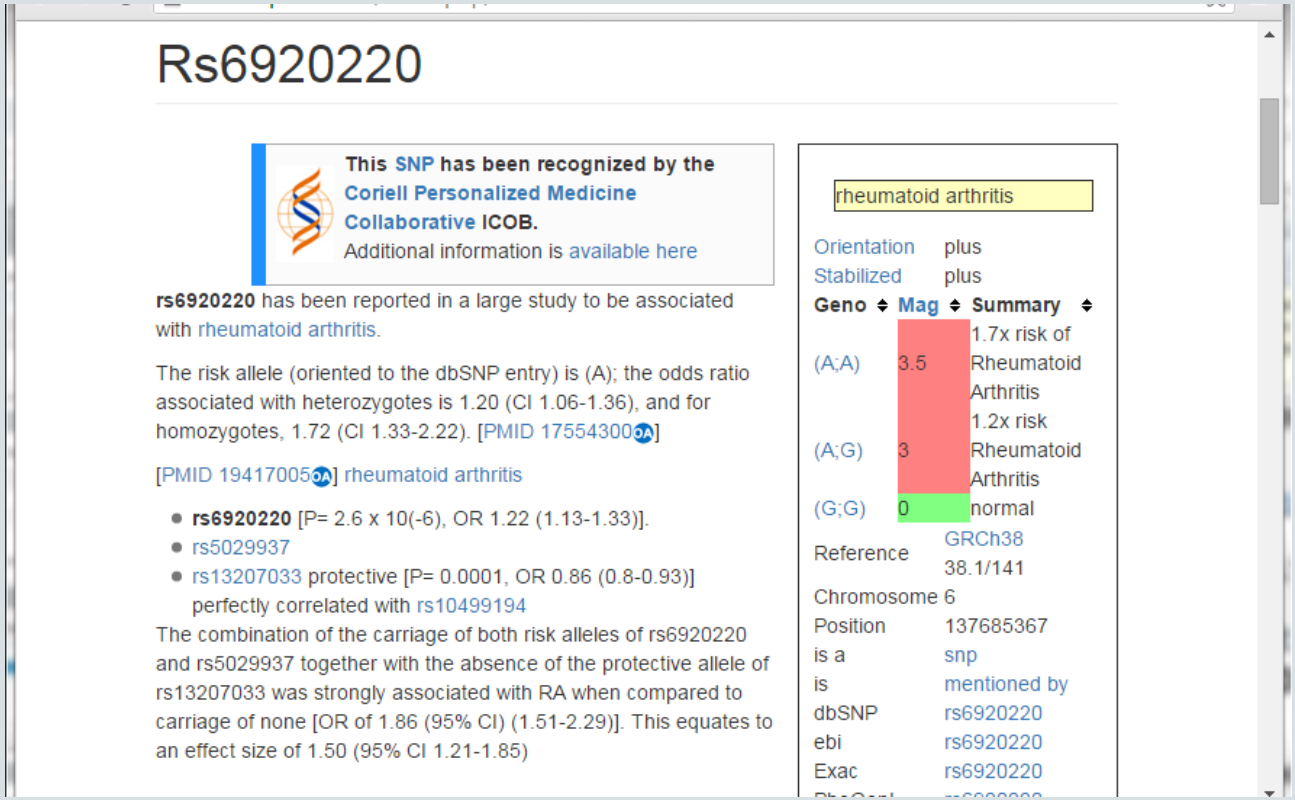
- I used these two tools to interpret my own 23andMe raw genetic data (Example: next two slides).

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.