Sharing / Reporting Genomic Results and Data

Outline

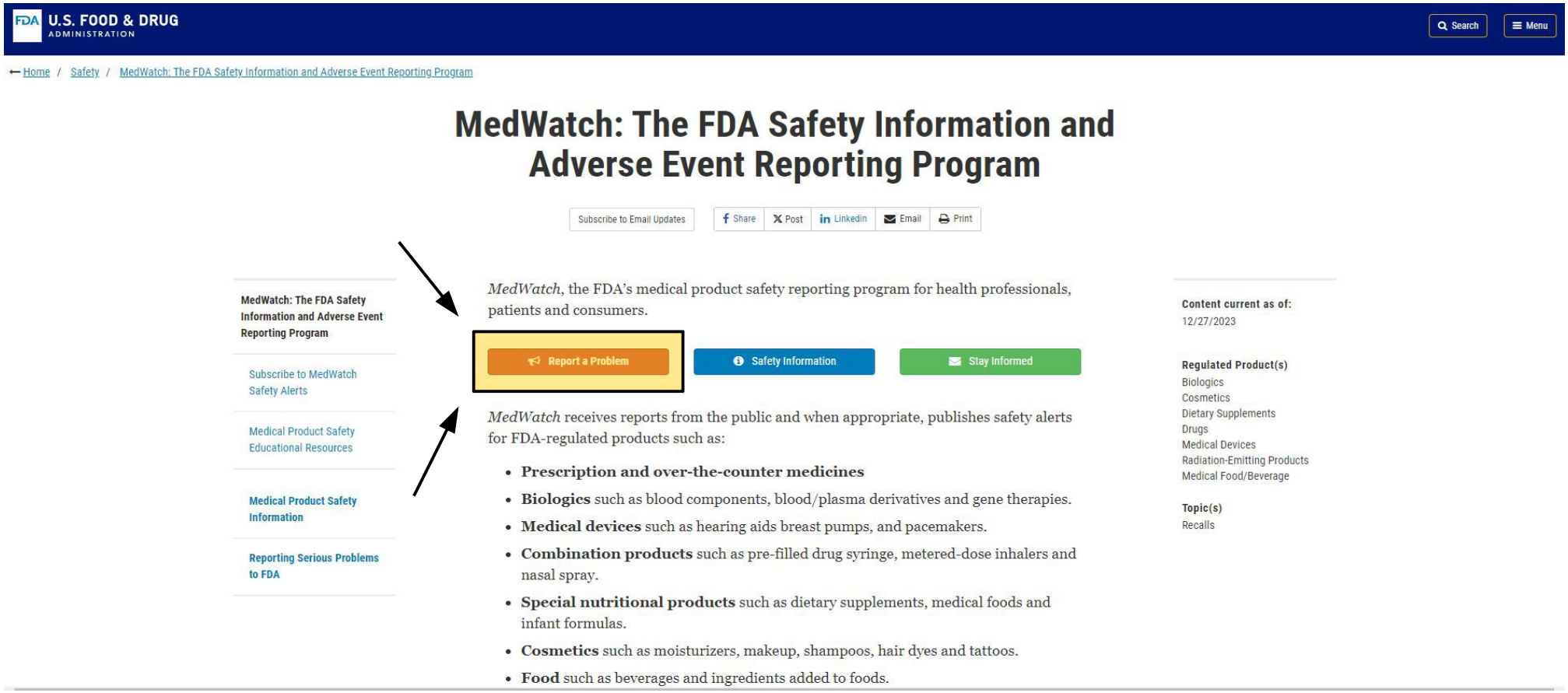
1) **FDA MedWatch Reports** ***(Any Medical Event)***

2) PrecisionFDA *(Raw Data)*

3) NIH ClinGen GenomeConnect *(Genetic Reports)*

FDA MedWatch Reporting

(*Step #1: Report a Problem*)



- While collecting information for recalls and/or reversal of FDA Approval may be a goal, FDA MedWatch can be used for products that are **not** FDA approved.
  - **In fact, most of my submissions would fall in that category.**

FDA MedWatch Reporting

(*Step #2: Consumer / Patient*)

MedWatch Online Voluntary Reporting Form

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Welcome

If this is a medical emergency, please call 911.
If you have a mental health crisis, please call 988.

Health professionals, consumers and patients can voluntarily report observed or suspected adverse events for human medical products to FDA. Voluntary reporting can help FDA identify unknown risk for approved medical products. Reporting can be done through our online reporting portal or by downloading, completing and then submitting FDA Form 3500 (Health Professional) or 3500B (Consumer/Patient) to MedWatch: The FDA Safety Information and Adverse Event Reporting Program.

While not mandatory, FDA encourages reporters to provide their contact information in case FDA needs to gather more information. Note that reporters can request, within the report, FDA not release their contact information to the manufacturer.

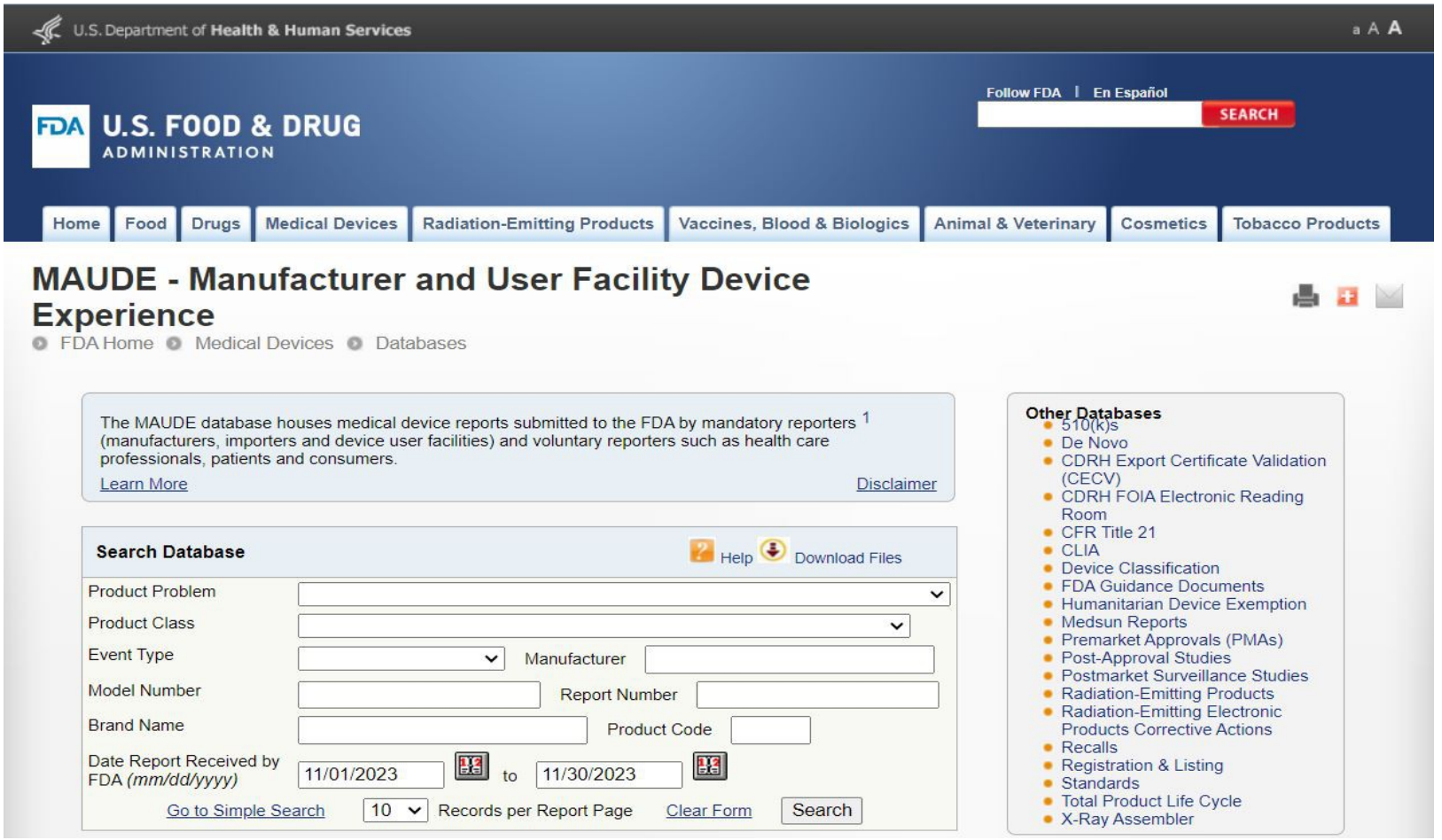
FDA MedWatch Reporting

(Step #3: Complete Report)

Please Note:

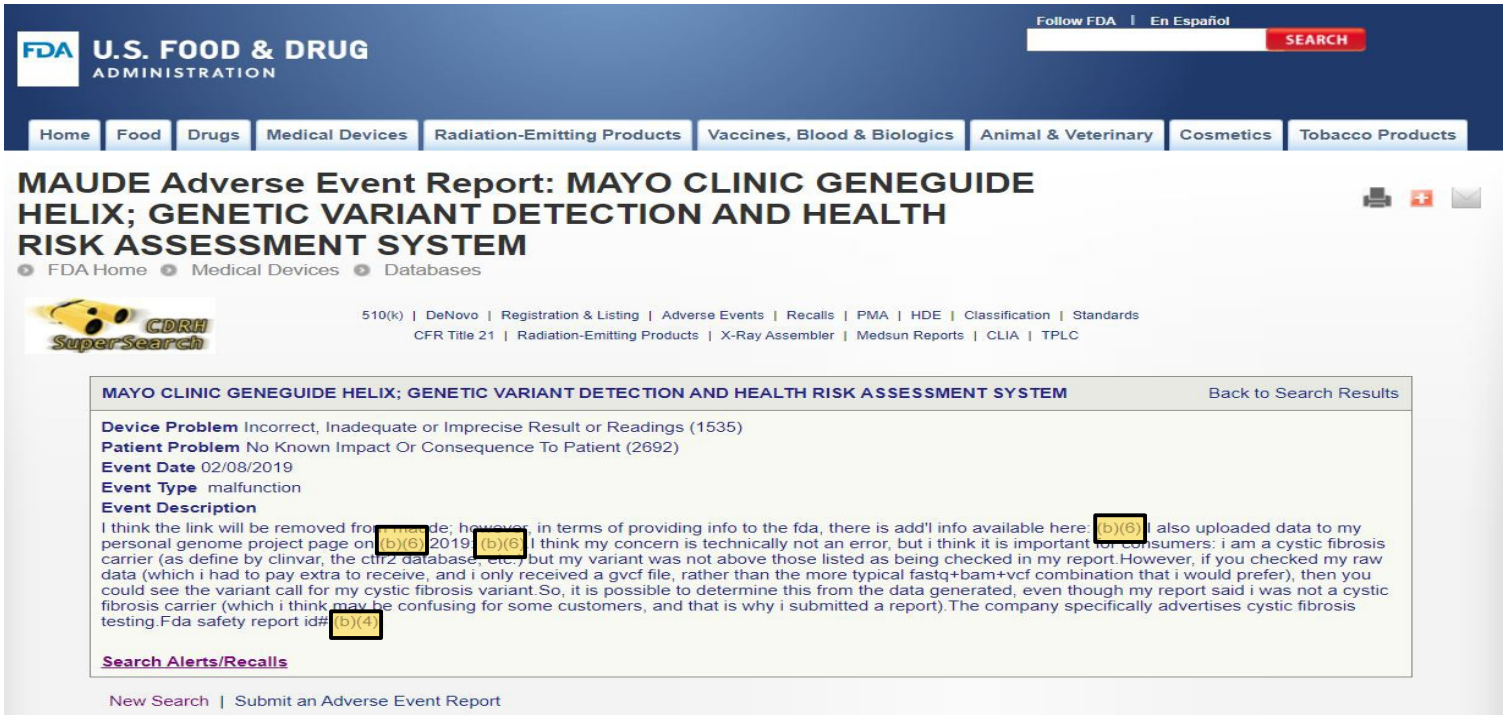
- If I have something important to report, then my expectation is that I can eventually submit a successful report. It is also possible to resume an incomplete submission.
- *However, your report might be accepted, and it may be helpful to save information for a re-submission.*
- You should be notified if your report is accepted. However, if the report is not accepted, then I don't believe that you will be notified (and you won't receive feedback to improve the submission).
- **If the report is accepted, then a de-identified version of the report should become available in the MAUDE database (*next slide*).**

FDA MAUDE Database
(for Accepted Reports)



- I will go through some examples in subsequent slides.

Mayo/Helix GeneGuide
(MW5093889)



FDA U.S. FOOD & DRUG ADMINISTRATION

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Home | Food | Drugs | Medical Devices | Radiation-Emitting Products | Vaccines, Blood & Biologics | Animal & Veterinary | Cosmetics | Tobacco Products

MAUDE Adverse Event Report: MAYO CLINIC GENEGUIDE HELIX; GENETIC VARIANT DETECTION AND HEALTH RISK ASSESSMENT SYSTEM

FDA Home | Medical Devices | Databases

CDRH SuperSearch

510(k) | DeNovo | Registration & Listing | Adverse Events | Recalls | PMA | HDE | Classification | Standards
CFR Title 21 | Radiation-Emitting Products | X-Ray Assembler | Medsun Reports | CLIA | TPLC

MAYO CLINIC GENEGUIDE HELIX; GENETIC VARIANT DETECTION AND HEALTH RISK ASSESSMENT SYSTEM Back to Search Results

Device Problem Incorrect, Inadequate or Imprecise Result or Readings (1535)
Patient Problem No Known Impact Or Consequence To Patient (2692)
Event Date 02/08/2019
Event Type malfunction
Event Description
I think the link will be removed fro[illegible]de; however, in terms of providing info to the fda, there is add'l info available here: (b)(6) I also uploaded data to my personal genome project page on (b)(6) 2019: (b)(6) I think my concern is technically not an error, but i think it is important for consumers: i am a cystic fibrosis carrier (as define by clinvar, the ctfr2 database, etc.) but my variant was not above those listed as being checked in my report.However, if you checked my raw data (which i had to pay extra to receive, and i only received a gvcf file, rather than the more typical fastq+bam+vcf combination that i would prefer), then you could see the variant call for my cystic fibrosis variant.So, it is possible to determine this from the data generated, even though my report said i was not a cystic fibrosis carrier (which i think may be confusing for some customers, and that is why i submitted a report).The company specifically advertises cystic fibrosis testing.Fda safety report id# (b)(4)

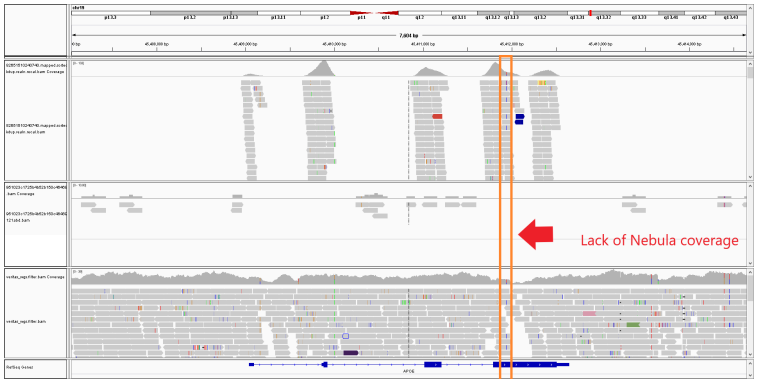
Search Alerts/Recalls

New Search | Submit an Adverse Event Report

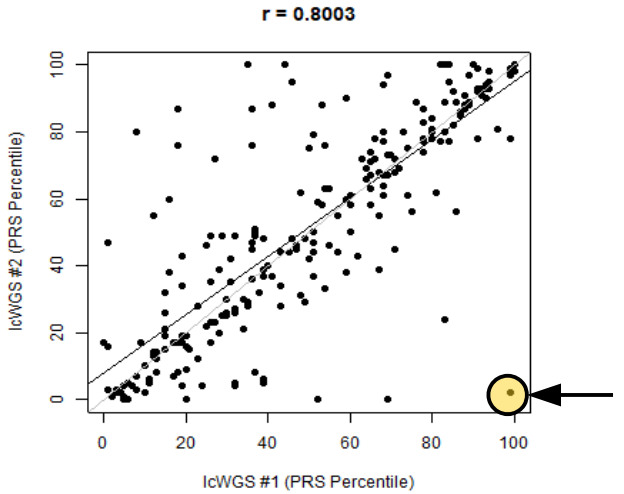
- I am a cystic fibrosis carrier, and this this was designed to test for variants causing this disease. However, I received a false negative result.
  - Link to Associated Blog Post
- For most examples, I am not sure if there are more recent changes (since original report, in this case in 2019).
  - However, this particular product has been discontinued.
- In the example above, you can see highlighted examples of de-identification. I am not sure about other formatting changes (such as a lack of capitalization within the sentences).

Nebula low-coverage Whole Genome Sequencing (lcWGS)
(MW5093887)

Inaccurate APOE Imputation
*(I am **E3/E4**, not **E3/E3**)*



PRS Concerns
(including replicate discordance)



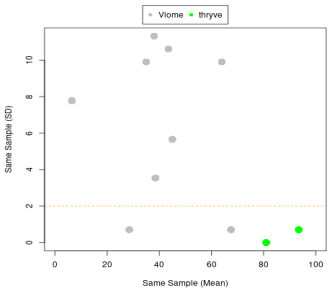
Replicate PRS percentile varies from **2%** and **99%**

- Link to Associated Blog Post
  - The scatterplot of PRS percentiles shown above can be found on this GitHub subfolder.
- In general, I am not sure about more recent changes (after 2019), and **my understanding is that Nebula currently emphases on higher coverage Whole Genome Sequencing** (such as 30x or higher, instead of ~0.5x or lower).
- *Other Polygenic Risk Score (PRS) Discussions*:
  - PRS results from other sources (described in this blog post).
  - I am attempting to apply iCARE breast cancer PRS to samples from myself here.

Viome
(MW5106218)

- There are multiple metagenomic posts. I have raw data for re-analysis from other companies, but not Viome.
- However, I believe that the outline of most relevant topics is provided in this blog post.
- I also submitted an FDA Regulatory Misconduct report related to describing being “approved” by the FDA, where you can see a draft for the submitted content here.
- Based in part upon what I show in the next slide (for a different company), **I did not take any action based upon recommendations from these reports**.
  - However, I believe discordance in results from replicate samples collected at the same is still noteworthy.
  - The blog post used for the dietary table on the left was also created for supplement recommendations (where I only noted variation in recommendations, without testing for adverse events).
- I have not collected more recent samples, so I am not sure what changes may have occurred after these 2021 reports.

Higher Variation for Replicate Viome Scores (with more total provided scores)



Viome Variation and Discordance from Current Helpful Dietary Changes or Preferences

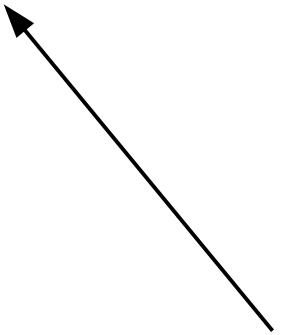
Viome "*Foods to Avoid*":

	Stool 1a	Stool 1b	Stool 2	Stool 3	Stool 4
Vegetables to Avoid	Bell Pepper Broccoli Brussels Sprouts Cabbage Mustard Greens Tomato	Bell Pepper Tomato	Bell Pepper Sauerkraut Tomato	Bell Pepper Tomato	Bell Pepper Cucumber Tomato
Proteins and Fats to Avoid	Almonds Chicken Egg Yolk Pistachios	Almonds Pistachios	Kefir (Cow Milk) Yogurt (Cow Milk, Plain)	Almonds Pistachios	Shrimp (Domestic)
Fruits and Grains to Avoid	*None*	*None*	Barley Blueberry	*None*	Watermelon
Other Food Items to Avoid	*None*	*None*	Coffee	Turmeric	*None*

I do drink tea instead of coffee, since coffee can irritate my eyes (and, at least to some extent, my stomach).

Vitagene
(MW5092056)

Reported Adverse Event
encountered after taking *L-Theanine*



Zinc supplement may have contributed to headache (at dosage available for generic)? ...I did not continue to take additional tablets.

In other words, Vitagene recommended that I take 7 supplements:

- *Bromelain Quercetin Complex (500 mg)*: Lifestyle (Joint health and Digestive health)
- *Probiotics (40 billion CFU)*: **Genetics (31%, *risk of Overweight, Hormonal support, Eczema, Allergies and Blood pressure health*, based upon 103 variants, all reported to have "Fair" research quality)**, Lifestyle (Everyday stress and Digestive health), and Goals (Everyday stress and Overweight)
- *Vitamin D (2000 IU)*: **Genetics (59% *Vitamin D Levels, Eczema and Joint health*, based upon 36 variants, all reported to have "Fair" research quality)**, Lifestyle (Everyday stress), and Goals (Everyday stress)
- *Theanine (200 mg)*: Lifesytle (Everyday stress), and Goals (Everyday stress)
- *Iron Free Multivitamin (10 Multi)*: Lifestyle (Energy and Nutrient intake levels)
- *Zinc (15 mg)*: **Genetics (50% *Overweight*, based upon 52 variants, all reported to have "Fair" research quality)** and Goals (Overweight)
- *Chromium (200 mcg)*: **Genetics (83% *Hormonal support, Overweight and Blood Sugar Health*, based upon 203 variants, all reported to have "Fair" research quality)** and Goals (Overweight)

- Related Blog Post
- I have not submitted new samples or checked for updates from the company after this post in 2019.
  - However, I believe from a source other than Vitagene, I see that there is a warning that I noted in the blog post: "*If you are currently taking prescription antidepressants such as MAOIs or SSRIs, consult your physician before taking this product*."
  - I was taking (and am taking) an SSRI.

Probabilistic Language from NIH All of Us Pharmacogenomics Report

Important! Genetic information is really just one piece of the puzzle.

- It won't tell us if a medicine will definitely work.
- It won't tell us if a medicine will definitely cause side effects or won't work at all.
- It won't tell us exactly how much medicine someone should take.
- It only applies to medicines that you eat, drink, or inject. It doesn't apply to medicines that are rubbed on your skin or used in your eyes or ears.

If your doctor has prescribed medicine for you, keep taking it. It can be dangerous to stop taking a medicine, or to change the dose or timing of it, without first asking your doctor.

- I will revisit this report in a later slide.
  - However, briefly, you can see my report uploaded here.

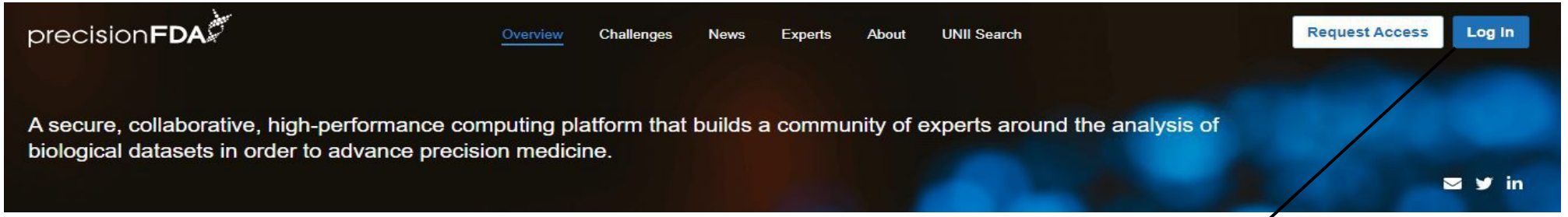
Outline

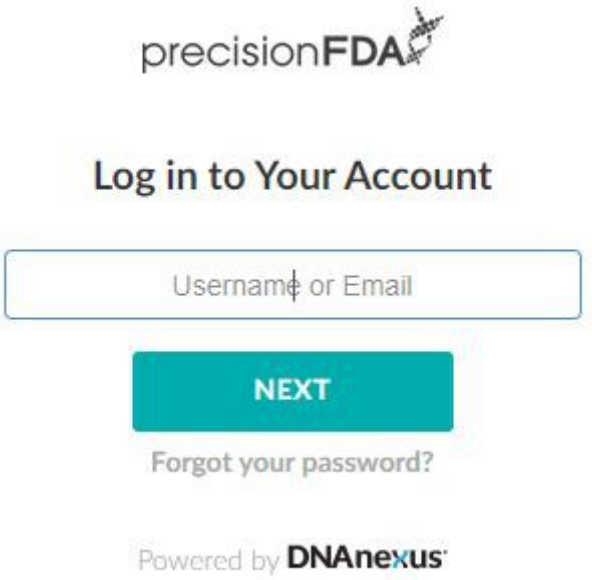
1) FDA MedWatch Reports *(Any Medical Event)*

2) **PrecisionFDA** ***(Raw Data)***

3) NIH ClinGen GenomeConnect *(Genetic Reports)*

PrecisionFDA Controlled Access Data Sharing





Experiences with Data Uploads

- There are web-based and command line options for data upload.
- At one point in time, I believe both worked for my account.
- However, most recently I believe the **web-interface** was *more successful* in being able to upload a **VCF** file with **variant calls**.
- For larger files (such as BAM alignment or FASTQ reads from Whole Genome Sequencing), I uploaded the data to Google Cloud and another developer created a URL Import function (url-fetcher): https://precision.fda.gov/home/apps/app-F0pyzk000GBvX7qVG137gV5Z-1
  - So, I think this experience may match others. Either way, I found this custom app to be very helpful.
  - That said, please note that there will probably be some **cost to uploading data to a Google Cloud bucket**. If you could directly upload to PrecisionFDA, then that should be free.

Outline

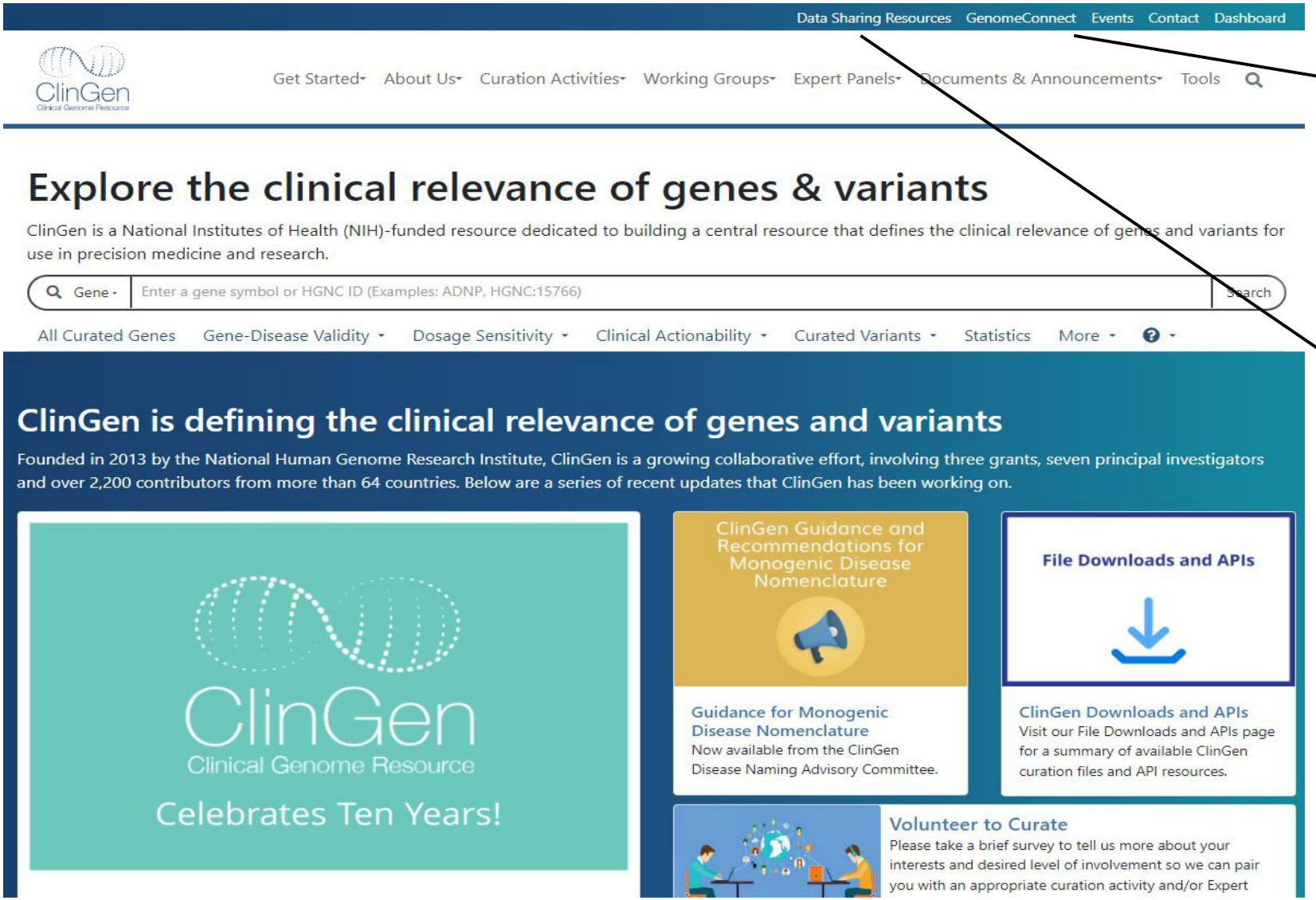
1) FDA MedWatch Reports *(Any Medical Event)*

2) PrecisionFDA *(Raw Data)*

3) **NIH ClinGen GenomeConnect** ***(Genetic Reports)***

...also includes some public data sharing with personal GitHub repository.

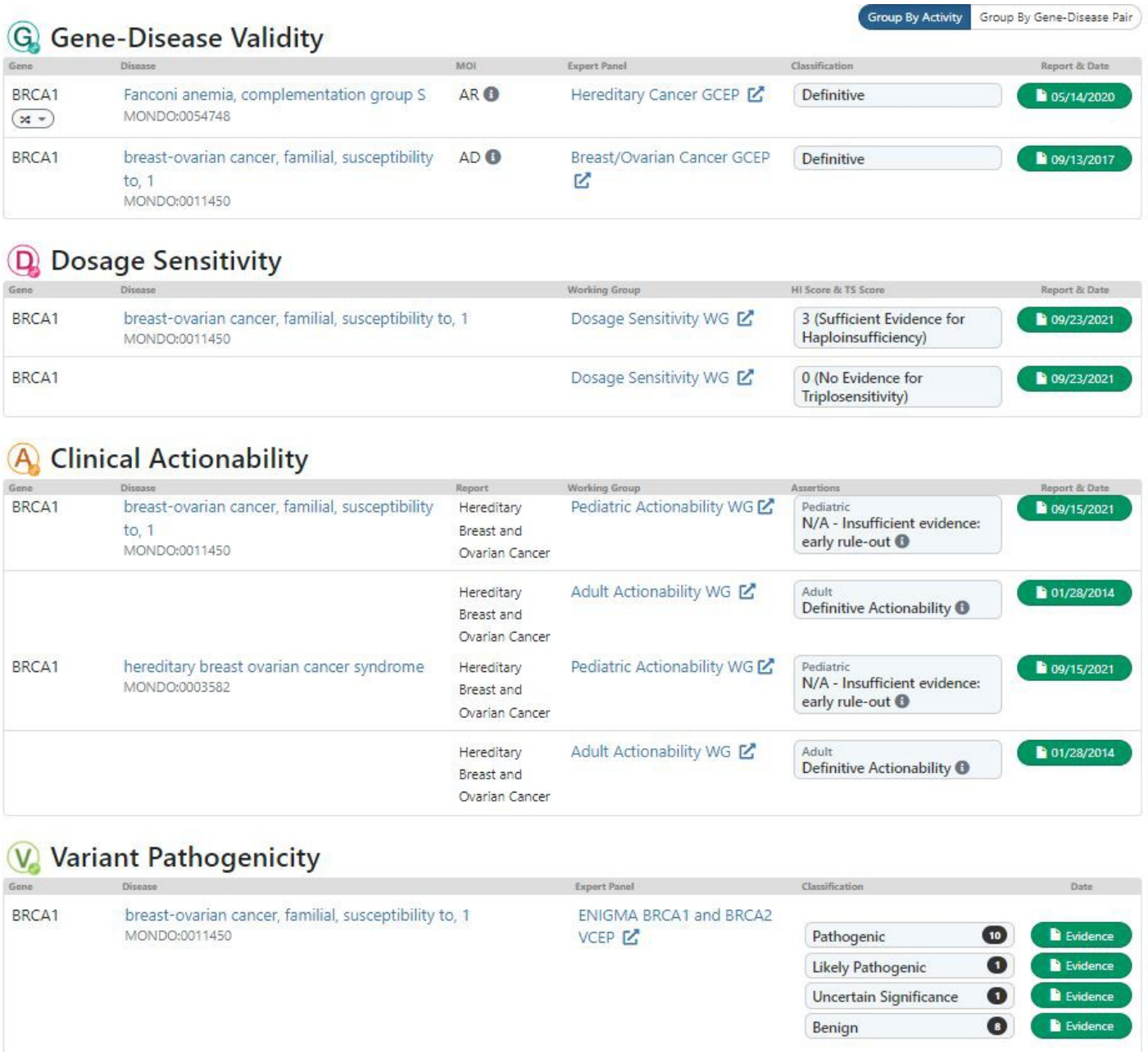
ClinGen



My understanding is that "**GenomeConnect**" provides options for **individual** genetic/genomic data sharing.

As of 1/ 1/2024, "**Data Sharing Resources**" provides information for **clinicians** and **laboratories** (for genetic/genomic data sharing).

BRCA1 ClinGen Screenshot



Group By Activity | Group By Gene-Disease Pair

Gene-Disease Validity

Gene	Disease	MOI	Expert Panel	Classification	Report & Date
BRCA1	Fanconi anemia, complementation group S MONDO:0054748	AR	Hereditary Cancer GCEP	Definitive	05/14/2020
BRCA1	breast-ovarian cancer, familial, susceptibility to, 1 MONDO:0011450	AD	Breast/Ovarian Cancer GCEP	Definitive	09/13/2017

Dosage Sensitivity

Gene	Disease	Working Group	HI Score & TS Score	Report & Date
BRCA1	breast-ovarian cancer, familial, susceptibility to, 1 MONDO:0011450	Dosage Sensitivity WG	3 (Sufficient Evidence for Haploinsufficiency)	09/23/2021
BRCA1		Dosage Sensitivity WG	0 (No Evidence for Triplosensitivity)	09/23/2021

Clinical Actionability

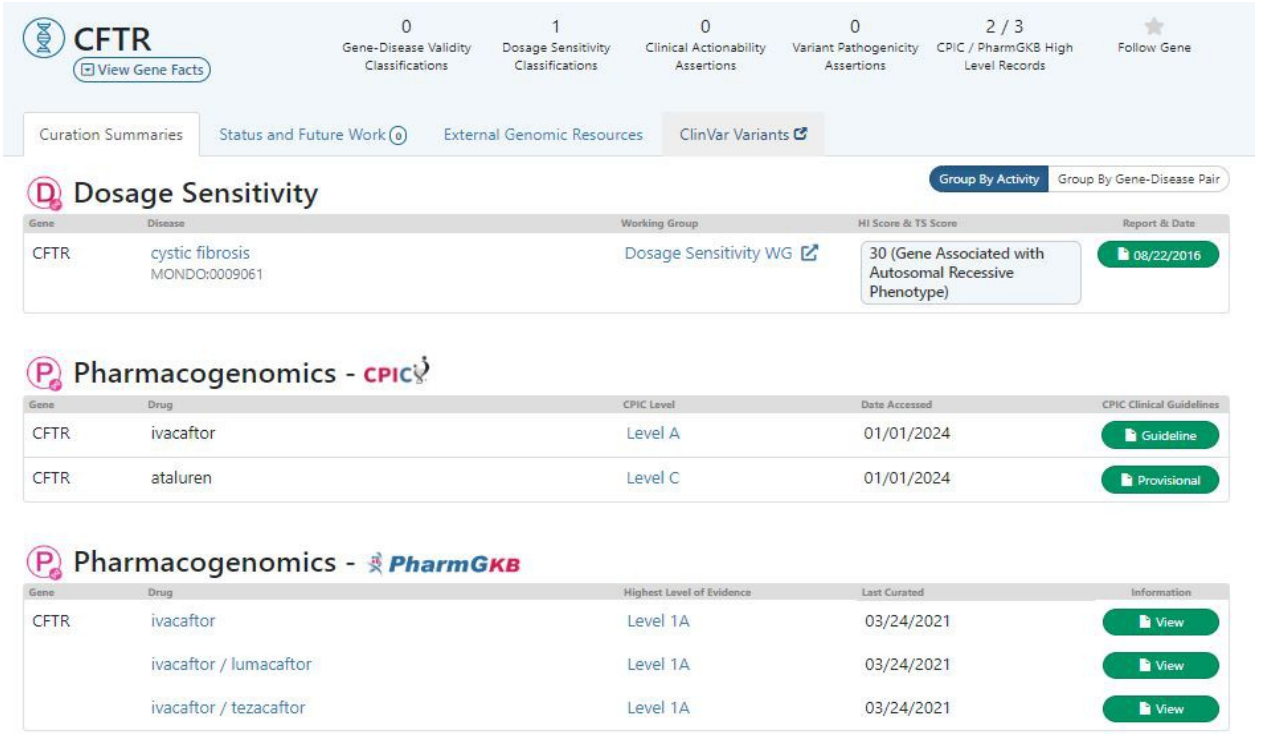
Gene	Disease	Report	Working Group	Assertions	Report & Date
BRCA1	breast-ovarian cancer, familial, susceptibility to, 1 MONDO:0011450	Hereditary Breast and Ovarian Cancer	Pediatric Actionability WG	Pediatric N/A - Insufficient evidence: early rule-out	09/15/2021
		Hereditary Breast and Ovarian Cancer	Adult Actionability WG	Adult Definitive Actionability	01/28/2014
BRCA1	hereditary breast ovarian cancer syndrome MONDO:0003582	Hereditary Breast and Ovarian Cancer	Pediatric Actionability WG	Pediatric N/A - Insufficient evidence: early rule-out	09/15/2021
		Hereditary Breast and Ovarian Cancer	Adult Actionability WG	Adult Definitive Actionability	01/28/2014

Variant Pathogenicity

Gene	Disease	Expert Panel	Classification	Date
BRCA1	breast-ovarian cancer, familial, susceptibility to, 1 MONDO:0011450	ENIGMA BRCA1 and BRCA2 VCEP	Pathogenic 10	Evidence
			Likely Pathogenic 1	Evidence
			Uncertain Significance 1	Evidence
			Benign 8	Evidence

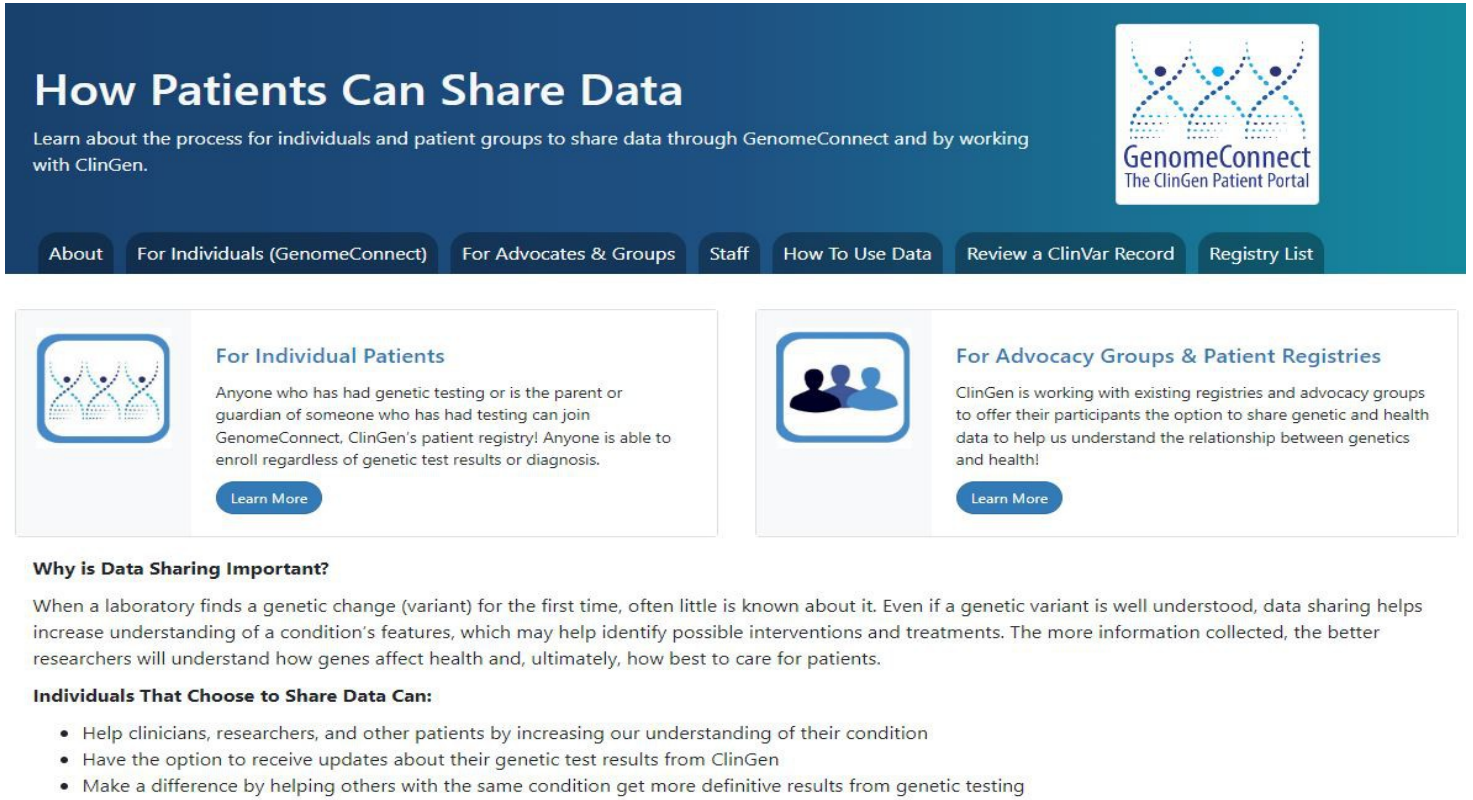
- You can see information from multiple sources are provided in ClinGen.
  - I believe that ClinGen "*Variant Pathogenic*" expert panel classifications are also submitted to ClinVar (with 3-star evidence).
- Please be aware that the ClinGen "***Variant Pathogenity"*** classifications from ENIGMA are **on-going**. For example, there are more than 20 variants for BRCA1.
  - In general, I believe BRCA Exchange is also a useful source of information.
  - I believe ENGIMA is also used as the source for clinical significance classifications for BRCA Exchange.
  - However, in ClinGen, you can see additional information available for c.135-1G>T (versus c.5212G>A, for example).

CFTR ClinGen Screenshot



- Again, you can see annotations from multiple sources is provided in ClinGen.
  - If you click the ClinVar link, you can see individual variants with a condition listed as “cystic fibrosis.”
- However, I don't see direct evidence for CFTR causing cystic fibrosis (which I would guess should be from within some similar categories as BRCA1 on last slide, even if this is *predictive* for autosomal recessive inheritance instead of a *risk* that can be described autosomal dominant).
  - Based upon assistance from ClinGen / GenomeConnect support, I believe this is because **a ClinGen expert panel evaluation has not been submitted**.

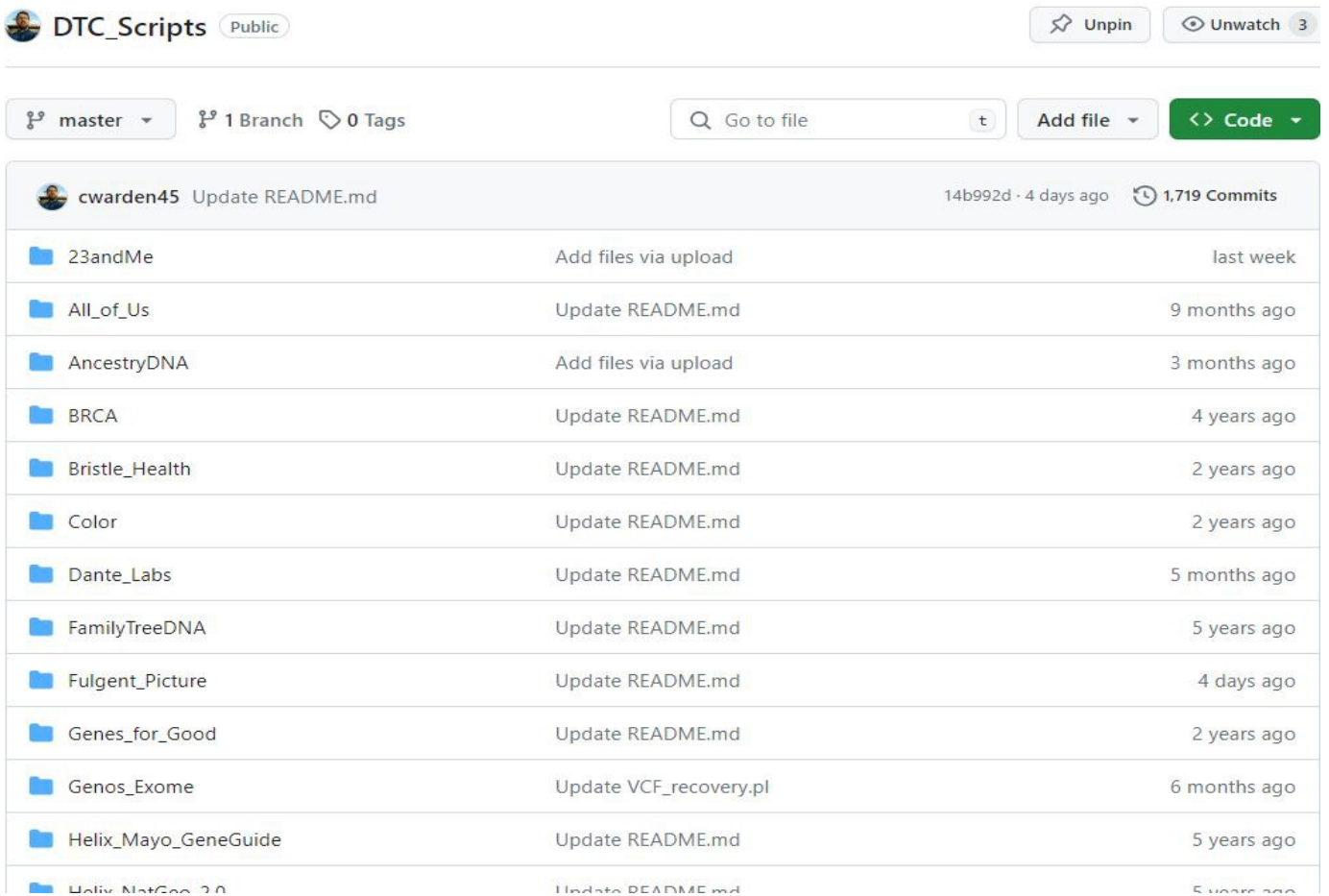
GenomeConnect for Individual Data Sharing
(Screenshot from ClinGen)



- More recently, I have encountered difficulties uploading additional data to my Personal Genome Project page (for hu832966).
- I can upload most of the similar content to a GitHub repository (and/or Google Cloud Buckets).
  - This is described in more detail on the next slide.
- However, that is less systematic data sharing than the Personal Genome Project (or PrecisionFDA, etc).
- **So, I was hoping that this could be an alternative from the NIH.**

DTC_Scripts GitHub Page
(Re-Analysis Code, Reports, and Small Datasets)

- Veritas Whole Genome Sequencing Code and Results can be found at the top level.
- However, “subfolders” (shown right) can be used to access content related to other companies or organizations.
- **I have also uploaded these slides** (available here)



NIH *All of Us* Pharmacogenomics Example

Medicine (Pharmacogenomics)

I **expanded** the details when creating the uploaded PDF, which includes **more details of what was tested** and **limitations in the results**.

There is a warning that **These medicines MAY BE impacted by your genetics.** Likewise, there are the following warnings (**bold font** added by me):

- *"It **won't** tell us if a medicine will definitely work."*
- *"It **won't** tell us if a medicine will definitely cause side effects or won't work at all."*
- *"It **won't** tell us exactly how much medicine someone should take."*

So, I think is good in terms of communicating some limitations in predictive power. However, it might have been nice if I could learn more about the variation in risk estimates (for absolute and relative risk).

In terms of a short summary:

Gene	Alleles / Type	Status	*Possible* Affected Mediciations
CYP2C19	*1/*1	**Normal** Metabolizer	
DPYD	*1/*1	**Normal** Metabolizer	
G6PD	B	**Normal**	
NUDT15	*1/*1	**Normal** Metabolizer	
SLCO1B1	*1/*15	Decreased Function (**may** increase your risk of developing muscle pain.)	simvastatin (Zocor®)
TPMT	*1/*1	**Normal** Metabolizer	
UGT1A1	*1/*1	**Normal** Metabolizer	

- In general, you can see summaries and re-analysis of results on the GitHub page.
- The above text is an example of me **parsing and reformatting** some content from my *All of Us* report.

GenomeConnect Homepage

Additional GenomeConnect Notes

- I used "*Other disease or health condition*" for myself, in order to complete registration.
  - In general, you can **find other participants** based upon diagnosis, gene, and/or geographic location.
- I do not have experience with my own variants, but my understanding is that GenomeConnect is capable of providing **free variant updates**.
  - However, please be aware that the timeline for updates is not certain.
  - Also, as explained by GenomeConnect staff, "*most participants will not receive updates and GenomeConnect does not identify all genetic updates.*"

Additional GenomeConnect Notes (...continued)

- Based upon Savatt et al. 2018, my understanding is that GenomeConnect helps meet the goal for ClinGen to assist with "*[supporting] data sharing.*"
  - Savatt et al. 2018 also describes potential benefits to adding and/or refining variant information for classifications in ClinVar.
- I believe that you can use *clingen@clinicalgenome.org* or *info@genomeconnect.org* to ask for assistance, which I found to be very helpful.

Thank You Very Much
for Your Interest!