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DNA Unicorn: An N-of-1 Community Advocacy Resource

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Background

Rare diseases are individually rare (affecting less than 200,000 people), and collectively affect millions of people worldwide (Institute of Medicine (US) Committee on Accelerating Rare Diseases Research and Orphan Product Development 2010a; NIH 2016; Shen et al. 2015). Currently, the number of known, rare genetic diseases is around 7000 and it is suggested that as many as 8000 rare genetic conditions have yet to be discovered (Dudding-Byth et. al, 2015; Lambertson, 2015).

Over the last several years, advances in technology have made whole exome sequencing (WES), a tool for diagnosing the previously un-diagnosable. In approximately 25-40% of patients tested, WES has identified the genetic basis of disease (Sawyer, 2016). WES created a paradigm shift in how both healthcare providers and researchers approach diagnosis of genetic disease (Sawyer, 2016). Using WES, researchers have identified more than 180 distinct novel disease-causing genes (Sawyer et al., 2016). However, rare variants within these genes are often labeled a "variant of uncertain significance (VUS)" due to insufficient data available to determine their effects on gene function and association with the patient's phenotype. To determine causality, functional studies can be performed, however these are expensive, fall outside the scope of clinical diagnostics laboratories, and are rarely covered by insurance. Identifying a second unrelated patient with overlapping phenotypic characteristics and the same variant can help link a variant to a disorder, but there is currently no established protocol for using databases to establish causality for these ultra rare diseases (Dixon-Salazar, 2012).

Due to the increasing use of whole exome sequencing, more individuals are now being diagnosed with extremely rare conditions not previously reported in the medical literature (hereafter referred to as "N-of-1" disorders) (Sawyer et al., 2016). N-of-1 diseases tend to be severe, life-threatening, debilitating, and affect multiple organ systems. Patients often present

with multiple problems that may seem unrelated, and unfortunately, for such rare diseases little is known about the natural history of the disease, and there are often no treatment or medical management guidelines (Dudding-Byth et. al, 2015). They can impair physical, mental, and/or behavioral capacities, and reduce one's life expectancy (Schieppati, 2008). For N-of-1 disorders, the variants and genes identified are by definition novel and unfamiliar, and may not allow access to scientific and medical expertise (Hennekam, 2011; Dudding-Byth et. al, 2015). Ultra-rare diseases, in general, lack management guidelines and information on natural history and prognosis (Dudding-Byth et al. 2015). More than 95 percent of rare diseases lack a specific treatment (Miyamoto and Kakkis 2011). However, a diagnosis validates the patients' symptomatology, provides information about prognosis and may offer hope for the direction of medical care in the future (Dudding-Byth, 2015; Krabbenborg et al., 2016).

The benefit of receiving a diagnosis extends beyond receiving specialized treatment. It also affords families the ability to understand and label the condition and better cope with the situation (Senger et al. 2016). A 2008 review in *The Journal of Clinical Genetics*, describes patients' adaptation to living with a genetic condition, and explores the process of coming to terms with the implications of a health threat, that "a diagnosis is initially disruptive and leaves parents or an individual feeling out of control. They seek ways to regain feelings of control by learning as much they can about the condition, taking control over aspects of medical care." (Biesecker et al., 2008). The emotional, medical, and psychosocial impact of rare diseases on the patient and their caregivers is compounded for those with N-of-1 disorders; parents become the real experts of these ultra-rare disorders and related therapies (Schaffer et al. 2008; Budych et al. 2012). Due to the low prevalence of each individual rare disease, parents of children with rare diseases report having high stress and emotional demands related to feelings of incompetence and social isolation (Dellve et al. 2006). The "surrounding psychological desert" is

distressing for N-of-1 individuals and their families, who cite a lack of support, even once they had received a diagnosis (Anderson et al. 2013; EURODIS 2009). Families impacted by a rare disease experience more psychosocial stressors than those affected by comparable, less rare conditions (Schieppati et al., 2008). The nature of the illness can present overwhelming challenges to parents who bear daily responsibilities for managing their child's care, while holding at bay this pervasive fear for the child's well-being, and experiencing feelings of guilt and personal failure (Senger et al. 2016). Furthermore, parents of children with complex medical conditions often carry extraordinary burdens, both visible and invisible, associated with care. Senger et al. describes how parents are called to advocate for their child while navigating a complex health care system, "The visible demands of caring for a chronically ill child […] include the technical day-to-day aspects of in-home medical care, sophisticated clinical judgment, and vigilant monitoring of symptoms. The invisible demands […] include worry and fear about the unpredictable nature of the illness trajectory, public reaction to the child's disability, and wondering how their child will fit into the world, gain acceptance, and make friends." (2016).

In the literature, a frequent theme described by parents as being essential was meeting other families with children diagnosed with similar conditions, and gaining a sense of control over an uncontrollable situation. Patients and caregivers tend to seek social support by joining support groups, striving to find ways to meet their own or their child's needs, which ultimately has been shown to be associated with positive adaptation across a variety of chronic conditions (Biesecker et al. 2008). A 2016 NPR article, "Families Isolated by Rare Genetic Conditions Find New Ways to Reach Out," centered on families affected by a rare genetic disease, and how they find ways to search for others with their same condition. The article explored families' sense of isolation; they described how having a child with an illness that is likely genetically based, yet never before described in the scientific literature, landed them in "an information desert." They

explained how research protocols tend to keep scientific findings quiet until they are published, or how health privacy laws prevent a genetics lab from connecting two families who have the same mutation. One parent noted, “These days there are ribbons and awareness weeks for so many diseases, […] but when yours is ultra-rare, you feel completely isolated. You feel like you're never going to hear another person say, 'Us, too!' And being connected to other families changes all that." (Snow, 2016). A recent 2016 study in the *Journal of Genetic Counseling*, examined the need for families to connect to other families with the same diagnosis, through the use of Facebook, social media, and other forms of online community support. One parent stated, “The information we have been able to get has been through other families […] We even had [an] awareness day earlier this month […] We are able to meet people that were 50 years old and that are diagnosed with [X] syndrome. You know, it is such a wonderful thing to be able to see sort of the future or the possibilities of the future.” (Rosell et al. 2016). The supports that would normally be provided by disease communities, which aim at gathering and disseminating the limited existing information on their disease, and connecting patients and families, do not exist or are not geared towards an N-of-1 diagnosis. For all these reasons, significant gaps exist for N-of-1 families.

Existing literature on rare diseases is highly disease oriented and technical, primarily originating from the research of medical specialists. Rare disease patients believe the information they receive from health professionals at the time of diagnosis is insufficient, thus motivating their engagement in online research (Gundersen 2011). Parents use of the Internet to search for information, and engagement in online communities are important ways parents often manage uncertainty and stress regarding their child’s health condition (Oprescu et al. 2013). It is estimated that 56.3 million people in the US use the internet to search for information about chronic diseases, and this information affects their decision-making regarding

their health (Dutta-Bergman 2004; Rainie et al. 2003). Approximately 79 million Americans are members of online support groups, with an estimated 1 in 4 people who join discussion groups while searching for disease information (Levy and Strombeck 2002; Rainie 2005). Individuals benefit from online health communities by receiving informational and emotional support, and many find the opportunity to share their own experiences and provide support to others rewarding as well. Cyber-based health forums allow families within a disease community to help one another identify specialists whose research is dedicated to a specific condition, and who may be willing to read an e-mail, give an opinion, or even possibly make an appointment for a consult (Eby, 2015). Patients who feel empowered have been shown to be more capable and effective at managing their health conditions, accessing care, and communicating with healthcare professionals (van Uden-Kraan et al. 2009). Online support communities offer several other advantages including lack of geographic restrictions, 24/7 availability, and a degree of anonymity (Oprescu et al. 2013a). Ultimately, there are few studies examining the impact of Internet support groups in the rare disease population, and even fewer catering to N-of-1 individuals specifically, thus highlighting the need for further research.

The goal of our project was to create a website that could be offered as a resource to individuals and families within the N-of-1 disease community. This resource would include user-friendly how-to guides that would help families navigate existing genetic databases and provide tools to advocate for themselves through social media campaigns. In constructing this website, we hoped to provide individuals with an N-of-1 diagnosis assistance in finding others in similar situations and establishing support communities.

Our Process

We believed it was important to provide families with a central resource that aggregated all existing resources. These families are often managing difficult lifestyles, balancing

busy schedules and family members' healthcare, and may not have the time to sort through resources, or know where to start. In order to make our website as useful and accessible as possible for visitors, we identified the ways in which individuals with a genetic disease and their families use the internet for information and support. We began by reviewing online resources currently available, and collectively assessed the benefits and limitations specific to the N-of-1 community for each resource. Many resources were found through Google searches, prior knowledge of resources through working with other genetic professionals, or previously successful support community initiatives by N-of-1 individuals and their families. Based on this analysis, we identified which websites to include and among those, which required step-by-step instructions. Primarily, these resources permitted individuals and their families to share their information online through various social media platforms or online databases that matched individuals based on their genetic information. For each resource that allowed individuals with an N-of-1 diagnosis to connect with others based on genotype or phenotype we created a how-to guide. Our goal was to provide a wide range of options to increase the chance of successfully connecting individuals or families.

There is a direct relationship between active participation on social media and the likelihood of making useful connections (Baruah, 2012). How-to guides for Facebook, Twitter, Wordpress, Reddit, and Wikipedia were all chosen to allow members with an N-of-1 diagnosis to create their own social media campaigns and empower them to tell their own story. We reasoned that these how-to guides are good starting points for N-of-1 individuals since most are already registered users of one or more. For individuals that currently do not use any social media the how-to guides aid them in setting up a profile on various social media platforms, begin potential promotion, and community building.

Another category of resources are databases that allow individuals or family members to enter specific genetic and/or clinical information, hopefully matching them with others from around the world. Since N-of-1 diagnoses are so incredibly rare, it is important to expand searches beyond a local geographical region. By participating in large-scale databases like MyGene2, GenomeConnect, and Undiagnosed Diseases Network, these individuals have the opportunity to be matched with someone from anywhere in the world. While these websites and databases can be useful for finding N-of-1 individuals, they are also difficult to navigate. They require a baseline understanding and ability to describe the condition, and genetic information that often requires the assistance of medical professionals and laboratories. We provide assistance through our how-to guides in making these resources accessible to N-of-1 families.

The last group of how-to guides included were online resources that could be used by the N-of-1 community to better understand their condition, and to keep up to date on any scientific research following a diagnosis. Many of these are potentially useful, but require scientific literacy and knowledge of specific nomenclature that could present an obstacle for many families or individuals. Therefore, we created how-to guides to be used as companion resources to Google Alerts, Human Phenotype Ontology (HPO) and PubMed.

Simplicity was key in the creation of the how-to guides, while still clearly describing a complicated process. How-to guides required multiple screenshots illustrating the step-by-step process one would take when navigating the resources. We wanted to ensure that the guides were easy to follow. This was done by including red arrows, boxes, and text boxes on the pictures so users would know exactly where to look to find the information required to move forward. Each guide was initially made by one group member, followed by multiple rounds of

edits by other group members and advisors. An example how-to guide can be seen in Appendix A.

Additionally, we provided brief resource summaries for SWAN, PEER, Global Genes, Rare Disease Day, ClinVar, ClinGen, OMIM, Genetic Alliance and NORD. We believe it was useful to bring an awareness to these resources for the N-of-1 community, but also recognized they were primarily geared toward other, more "traditional" rare disease audiences, healthcare professionals, researchers, and clinical laboratories. While our primary goal was to focus on resources that would help connect N-of-1 families to each other, we also wanted to put other carefully selected, relevant educational and informative resources in one place. We also provided an external link to the NIH's genome.gov, a web-based tool that provides a thorough and detailed genetics glossary. We felt it could be beneficial for individuals in the N-of-1 community to strengthen their understanding about genetics.

When naming the website and identifying potential branding opportunities, we wanted to find something that would encompass the uniqueness of individuals in the N-of-1 community. We also wanted a name that could become a symbol for the community as a whole. While researching available resources, we read many patient stories to better understand what some of these individuals and their families experience. The unicorn embodies the hopeful thought that even though you have not met someone with your disease, it does not mean they do not exist. It is also a symbol that equates rareness with something special and beautiful, rather than isolation and bad luck.

Once we established a name and logo for the website, DNA unicorn, we researched potential website domains. Our top priorities when choosing a website builder was ease of use and price point. Potential website builders we evaluated were Squarespace, Wix, Weebly,

Wordpress, and eHost. We chose Squarespace because it was relatively user-friendly, and provided video tutorials, as well as additional links to help navigate the system. Squarespace provided dozens of templates to choose from, thus enabling us to customize the website to our needs. These customizable templates provide a certain level of control, and come with built-in integrations, so that adding plug-ins, links, and files like PDFs, can be done directly on the website. Our focus when picking a template was to choose one that allowed us to upload multiple PDFs into one page while still being able to organize them neatly in an order we felt most desirable. Squarespace also offers free unlimited hosting, meaning there is no limit to the site's storage and bandwidth. This was important for any potential future growth of DNA Unicorn. Lastly, of the many domains we researched, Squarespace was one of the most affordable, providing a student discount with a two-year subscription.

Upon completion of the website, a beta version was sent to fourteen genetics healthcare professionals for their feedback. We received feedback through a seven-question survey. We asked participants to evaluate the aesthetics, language and content of the website, and of the specific how-to guides. Based on the feedback that we received, we incorporated appropriate changes to the website.

Below we will discuss each resource that is featured on our website, their purpose, strengths, limitations, and utility within the N-of-1 community.

Matchmakers

MyGene2: https://www.mygene2.org/MyGene2/

MyGene2 is a patient portal designed to assist families in finding a community of those with the same rare disease diagnosis. MyGene2 can be accessed by families, clinicians, and researchers to input medical and genetic information that can be shared with others. Families

and the MyGene2 matching system can search up to date profiles to look for matches based on phenotype, gene mutation, or ideally both. Furthermore, MyGene2 is linked to Match Maker Exchange (MME). MME is a large patient database that increases the chance of finding a match since it searches through a larger pool of affected individuals.

Because both families and healthcare professionals can access MyGene2, it can be a good place for a variant or candidate genes to be confirmed as the cause of a condition. If MyGene2 matches families with the same candidate gene or overlapping clinical characteristics, researchers who access the database can interpret the pathogenicity and causality of that particular gene or variant, and subsequently study possible genotype-phenotype correlations. Confirmation of a diagnosis allows healthcare professionals to provide more appropriate expectations and medical management, thus informing and assisting families' medical care and decision-making.

While MyGene2 is relatively easy to navigate for N-of-1 families, problems can arise when submitting genetic information. MyGene2's application form and instructions use scientific language that may be challenging for families to understand. Because of the complex nature of the genetic test results, and the language used on MyGene2's application, there is room for error or misinterpretation when submitting the information. This poses a problem, as the matches rely on the accuracy of the genetic information provided. To ensure the information entered matches both their genetic test results and clinical picture, and thus assuring an appropriate match, families may need to seek the assistance of their healthcare provider

The Undiagnosed Diseases Network: https://undiagnosed.hms.harvard.edu/

The Undiagnosed Diseases Network (UDN) is targeted to those individuals who have yet to receive a genetic diagnosis explaining the cause of the symptoms they experience. This patient population is affected with disorders that have not been diagnosed using conventional genetic testing methods.

The UDN's goal is to encourage collaboration between clinical and research experts at top institutions across the United States, and to solve challenging undiagnosed cases that burden individuals and families. The UDN aims is to help individuals and their families understand the nature of their disease and to connect with others who are similarly affected.

When submitting an application, the UDN system is simple to navigate for families without a science or medical background. Additionally, the UDN provides great resources that outline topics including the genetic testing process, and how to find similarly affected individuals online. One drawback of the UDN system and application process is that patients and their families require supporting documentation from their healthcare provider. Providers must have a referral letter outlining previously completed testing and a summary of the patient's symptoms. While this ensures a higher percentage of applications are appropriate for the overarching goal of the UDN's mission, it can be a barrier for families who wish to enrol but whose providers did not submit the required information.

As more individuals are completing applications and being accepted into the network, there is an ever-growing list of candidate genes being discovered. While the main goal of the study is to increase understanding about the genetic contribution to human disease, the UDN makes an effort to support families following a diagnosis. UDN recognizes that having a rare diagnosis is isolating and taxing on families, and works to combat that through social media exposure (Dellve et al. 2006). Once a diagnosis is confirmed, UDN will assist families in creating a

profile that will outline their symptoms, diagnosis, and personal stories. Families are consulted about how much or how little information they are comfortable sharing and once completed by the UDN, that profile can be shared on their website and various social media platforms (i.e. Reddit, Facebook, and Twitter). The profiles created by the UDN are similar to ones we have outlined in DNA Unicorn through how-to guides. The limitation of social media campaigning through UDN's platforms is that they can only be discovered when looking at the UDN website or social media pages.

GenomeConnect: https://www.genomeconnect.org/

GenomeConnect is an online registry and database that allows users to securely and confidentially share their health data and genetic test results. By sharing information through GenomeConnect, users add to the knowledge base of genetics, health, and the relationship between the two domains. This knowledge assists physicians and researchers in understanding the genetic basis of certain diseases and aids in the development of treatments. GenomeConnect now has a Participant Matching System that users can opt to join. The Participant Matching System helps users connect and find others with a similar diagnosis. GenomeConnect is open to all adults (18 or older) and users must meet one of the following criteria: have already had genetic testing, are considering genetic testing, or are family members of someone who has had genetic testing. This resource, alongside MyGene2, is one of few that exist for the purpose of matching users based on genetic and phenotypic data using a secure portal. It can be time-consuming for users to enter phenotypic data, especially if multiple organ systems are involved, but this is necessary in order to best match with others.

The Participant Matching System is a new part of the GenomeConnect resource, which means that at this time the number of enrolled users is likely still relatively small. Additionally,

because this is a newer feature of GenomeConnect, fewer health care providers are aware that it exists and may not be directing their N-of-1 patients to the website. The more people participate, the more the database will grow, increasing the number of matches. This resource appears to only be available in English, so users around the world may have difficulty accessing GenomeConnect. It will be important to engage users around the world, especially with N-of-1 diseases because of the extreme rarity of each individual disease.

PEER: http://www.geneticalliance.org/programs/biotrust/peer

Platform for Engaging Everyone Responsibly (PEER) is an online platform offered through the Genetic Alliance that allows people to electronically share their health data for research. Anyone, regardless of his or her current health, can register and enter health data. Physicians and researchers also register to be a part of PEER and create profiles so that participants understand their areas of research and practice. Participants can decide which researchers, physicians, and organizations are allowed to access their contact information and data, and what specific data they can have access to. Participants are able to change their access settings at any time. Different disease advocacy organizations can create their own portal and community within PEER. Participants can register for PEER through an existing disease organization portal or as an individual independent from an advocacy organization. PEER can be used by participants to connect with researchers and physicians who have research interest in a specific gene or type of disease and help add to their knowledge base. Through PEER participants may also find a clinical trial or physicians that have expertise in treating a specific type of disease. PEER has community-based examples to help users decide what information to share. The community-based examples are guides developed by PEER users affiliated with specific disease advocacy organizations to help people choose their privacy settings. At this point PEER only has around 45 disease-specific communities. N-of-1 families would have to sign

up as an individual, a feature that currently offers less guidance on registering and selecting privacy settings. While PEER has the potential to be an excellent resource for many N-of-1 families, it is currently being updated and the link to register for PEER as an individual is currently unavailable.

Social Media

Social media is a type of electronic communication using websites and applications that allow users to create and share content, and to network with others. Social media websites are useful for sharing personal stories and campaigns across the world for free. They can be accessed anytime, by anyone with a device or personal computer, and anywhere as long as an Internet connection or mobile network is available. The story of Bertrand Might is an example of how social media can be used successfully to share a rare disease story in order to identify other individuals with the same gene and phenotype to create a rare disease community (Mnookin, 2014). When Matthew and Cristina Might's son Bertrand was diagnosed with an N-of-1 genetic disease, Matthew wrote a powerful online essay on his already popular blog detailing his family's experience and shared it on Reddit (Might, 2012). Within 24 hours the essay had gone viral, was shared on several social media websites, and was the top story on Reddit (Mnookin, 2014). Through sharing his family's story, Matthew Might was able to find other individuals around the world with the same genetic disease as Bertrand, thus creating a community for himself and others. To help other families utilize social media to effectively find others with the same N-of-1 disorder, we created how-to guides for four popular social media websites: Facebook, Twitter, Reddit, Wordpress (blogs), and Wikipedia.

Facebook: https://www.facebook.com/

As of July 2016, Facebook had 1.71 billion monthly active users worldwide (Fiegerman, 2016). Anyone with Internet access and an email address or phone number can create an account on Facebook, although there are minimum age restrictions in some locations. Users can send "friend" requests to other users, which allows them to see each other's posted content. Registered users are able to post text, pictures and videos, files, privately message others, and join private or public interest groups. The ability of anyone to create a group is especially useful for N-of-1 families because they can use this function to create their own support communities. The person who creates a group has the ability to decide who can join and what content is shared within the group. Also, there are privacy settings that can be adjusted to allow only group members to see the content shared on the group timeline. This is particularly useful when discussing personal health information or posting photos of minors.

Facebook has a help center that explains its many features and applications in a simple way. It is easy to set up a personal account and a group in minutes. As with most social media, some individuals may post controversial and offensive content. A Facebook user does have the ability to report offensive content and block those individuals who post it. Another limitation is that messages are only seen by friends unless they are shared. If a user does not have very many active Facebook friends their message may not make it very far. A Facebook post can be made "public" allowing any Facebook user to see it, which could help individuals reach a wider audience.

Twitter: https://twitter.com/?lang=en

Twitter is a social media platform where users post content, called "tweets," to their timelines. Tweets are limited to 140 characters and can be linked to articles and videos. Users can follow others and be followed, and you are able to view many accounts without being a

registered user. Registered users can "reply" publicly to another user's tweet and direct private messaging is also available to individuals who follow each other. In addition to social networking, Twitter can also be used to find out about current events and news from around the world. As of June 2016 Twitter had 313 million active users (https://about.twitter.com/company). Organizations can also create Twitter accounts to interact with and keep their followers up to date on the organization. Making a Twitter account takes very little time. For those who want it, Twitter allows for some degree of anonymity because sharing personal information is not required. On Twitter, users can search for topics of interest and see tweets pertaining to a particular topic. For N-of-1 families, Twitter could be another way to share their stories, to search for others, and to stay updated with news and events from rare disease organizations. While Twitter is useful for staying updated on current events, Twitter must be checked frequently, especially if following multiple accounts as their timelines will be constantly changing. Additionally, a tweet is limited to 140 characters, so users must be succinct and thoughtful about word choice to maximize the impact of a tweet. It can be difficult to tweet about more detailed or complicated subjects.

Reddit: https://www.reddit.com/

Reddit is a platform that allows it's online community to rate and discuss web content posted by its users. According to recent Reddit web traffic statistics, as of November 2016, Reddit had over 100 million monthly visitors (12 million unique users) (https://www.reddit.com/r/AskReddit/about/traffic/). The website has a rating system that allows registered Reddit users to "upvote" or "downvote" content based on their opinion of whether a post contributes to the conversation or not. Per Reddit, "Through voting, users determine what posts rise to the top of community pages and, by extension, the public home page of the site." (https://reddit.zendesk.com/hc/en-us/articles/204511479-What-is-Reddit-).

Content ratings will determine the level of success and visibility each post receives. There are discussions and posts on Reddit that cover a large number and wide range of subjects. Reddit is different compared to other social media platforms in that by voting, the users have an active role in deciding the content that appears at the top of each page (this is the content that is the most popular). Furthermore, in Reddit users can participate in open discussion forums with more anonymity than Facebook. With Reddit it is easier to have a discussion about a particular topic than it is on Twitter because the user is not limited to a 140-character post. Reddit can be a good source for sharing complex personal stories and creating a common interest community. The example of Matthew Might illustrates the power of Reddit in sharing a story around the world. However, Reddit is not user friendly and it takes a significant amount of time to learn to use all of its features. Additionally, there are certain parts of Reddit that are not accessible unless the user has enough "Karma points", which are gained through consistent use and voting on posts. A user has to be sufficiently active in the Reddit community to gain the Karma points, meaning they have to make a significant contribution to the site before being able to access the full benefits of the platform.

Wikipedia: https://www.wikipedia.org/

Wikipedia is an online encyclopedia that is written by people individually or in collaboration. Wikipedia is a resource that N-of-1 families can utilize to distribute information about a given condition. Individuals can share educational information about gene structure and function, or the symptoms, management, and possible therapies of a defined disease. The hope for N-of-1 families is that a Wikipedia page can educate people who search for the gene or disease. Wikipedia is a great platform for these families to start with as it is used on a global scale, and places near the top of most Google or other search engine results.

Wikipedia does pose some challenges for first time users, specifically regarding the guidelines for what is and isn't allowed. Wikipedia does not permit users to create a Wikipedia page about themselves for any personal campaign. Therefore, if users are affected by an N-of-1 disease and decide to create a Wikipedia to share their story, they would be in violation of the websites policies. Affected individuals can work around these restrictions by creating Wikipedia pages about the gene or condition they are affected by. Wikipedia does allow individuals to create pages about other people. Therefore, families can create Wikipedia pages about the gene change that caused an affected family members symptoms and their journey to finding a diagnosis and effective management.

Wikipedia is relatively simple to use in its most basic format. It is a resource that all families should be able to utilize to promote their condition in order to create an N-of-1 community. When adding additional features to the Wikipedia page some coding is required which complicates the process considerably. Coding is required to change the font or color of the text, as well as to insert images, video, and other links. These features are fundamental to creating an effective Wikipedia that captures an audience when establishing an N-of-1 community.

Blogs: https://www.wordpress.com/

Blogs were created to allow individuals to express themselves online in a form of an online journal. Since then, blogs have evolved into a platform for company press releases, artist portfolios, a space for businesses to engage their clientele, and countless other purposes. Using a blog to document one's life gathers like-minded curious readers. As blog sites have developed, bloggers are able to establish connections with their readers and create virtual communities. There are a myriad of different blog-creating websites that allow users to create blogs that suit

their needs. Often these blogs range from the free and easy to use, to more complicated versions with monthly fees. These websites provide a domain name, templates, and blog builders that allow users to customize their blog based on their needs and personal style. Creating a blog can be overwhelming, but the process is simplified when choosing a website builder with easy to use templates and clear instructions. Regardless of the blog users choose, there will always be some degree of trial and error involved in the creative process. Our how-to guide focused on using Wordpress to create a free blog. Despite the free templates being simple, and not having options available to those with a monthly fee (i.e. removing Wordpress advertising, site storage, monetizing abilities, and advanced design tools), it is sufficient for the purposes of spreading awareness regarding N-of-1 diseases and establishing support communities.

Once users have created their blog, it needs to be continually edited to suit their changing needs, as well as updated with new content to allow readers to view and follow their journey. For N-of-1 families, blogs can be used to share their diagnostic odyssey, daily struggles, and triumphs in order to form connections with similarly affected individuals. A blog can also be used as a therapeutic outlet. Blogs work best for these individuals and families when they are open and forthcoming with personal genetic information and stories regarding their diagnosis. The more information provided, the more likely someone will read it and correctly identify themselves as being similarly affected. Blogs can be beneficial in that they allow one's struggles to be heard, but the ultimate aim of the blog how-to guides was to facilitate the blog's ability to build a community.

Scientific Literature and Databases

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/

PubMed is a free, searchable, online database that houses abstracts and links to publications in the life and biomedical science literature. While PubMed is a valuable resource that is updated daily by the United States National Library of Medicine and the National Institute of Health. Its target audience is healthcare providers, researchers, and those in academia. PubMed is more successful when one knows what they are searching for and can enter in search terms that yield appropriate results. Success with PubMed is minimal when the user is entering combinations of keywords on a trial and error basis. For many N-of-1 families, this trial and error process is their only option. This is further complicated by the fact that PubMed does not freely supply the literature in its library to all users. Many journal articles come with a hefty and unrealistic price tag for the average N-of-1 family. Those who remain undiagnosed are able to search combinations of unique clinical identifiers in the hopes of finding literature on a condition that matches theirs. However, this approach is often unsuccessful and time consuming. For those who do receive a genetic diagnosis following testing, that genetic variant can be searched within PubMed, and the results may provide a good starting place if families are interested in contacting researchers or following developments in the field. The weakness of PubMed is that it does not cater to a lay audience, thereby limiting the use of its extensive library for most of those with N-of-1 disease. Lay users may find it helpful to share their findings on PubMed with their healthcare providers assistance.

Gene Reviews & OMIM: https://www.ncbi.nlm.nih.gov/books/NBK1116/ ; https://www.omim.org/

Gene Reviews and Online Mendelian Inheritance in Man (OMIM), much like PubMed, are resources that are likely to be challenging to understand for individuals who do not have a background in clinical and molecular genetics. GeneReviews is an international point-of-care resource tailored to busy clinicians that provide clinically relevant and medically actionable

information about inherited conditions. OMIM is a well-referenced online catalogue of human genes and genetic disorders. Both resources contain an extensive library of well documented, peer-reviewed, and up to date information on genetic conditions or genes associated with medical conditions. However, by definition, N-of-1 genetic conditions are absent from the literature due to a lack of any well-documented cases, as well as uncertainty as to the pathogenicity of candidate genes.

Additionally, these resources' target audience is medical professionals and researchers. While Gene Reviews does feature drop-down boxes that provide simplified definitions for various words to accommodate a lay audience, information may be too complicated for the average individual. OMIM pulls together the published literature and research regarding on a particular condition or gene, which unfortunately does not always apply to N-of-1 conditions. Of the information OMIM does provide, much of it would not be appropriate for a lay audience.

HPO and Phenomizer: http://human-phenotype-ontology.github.io/: http://compbio.charite.de/phenomizer/

The Human Phenotype Ontology (HPO) is a project in partnership with the Monarch Initiative that is directed at standardizing the medical/scientific terms used to describe phenotypes associated with human disease. The initiative uses the scientific and medical literature, and resources such as OMIM, DECIPHER, and Orphanet to build the HPO database. Each of the terms in the HPO describes a specific phenotypic feature, and is associated with a list of synonyms that includes the "lay person" terms commonly used to describe the feature. A definition of the term is often included. The HPO was designed for use by clinicians and scientists; however, the HPO is available to freely use online and may be helpful for N-of-1 families when trying to determine medical terms to describe the affected individual's

phenotypic features. The HPO has approximately 11,000 terms as of Feb. 2017 with new terms continually being added (http://human-phenotype-ontology.github.io/about.html). The HPO is difficult to navigate and use; it takes a significant amount of trial and error for the user to understand how to efficiently use it. Additionally, not all terms in the HPO have had a definition added to their respective pages yet. That being said, this resource can be helpful when entering data into matchmaking databases such as GenomeConnect or MyGene2 to ensure that standard terminology is being used when entering phenotypic information.

The Phenomizer is a database of diseases that can assist in the diagnosis of a disease based on phenotype. HPO terms are applied to the diseases that are in the Phenomizer database. The Phenomizer was designed to assist physicians in creating a list of differential diagnoses during a diagnostic work up. Entering the phenotypic features of a patient produces a ranked list of possible diagnoses. Again, this tool is freely available to the general public so it can be accessed by anyone, but it is most useful for individuals who are more scientifically inclined. The Phenomizer may be used by individuals and their families who are still searching for a definitive diagnosis that explains their phenotype. Like the HPO, the Phenomizer is difficult to use and is easier to navigate/understand if the user has a medical background. If people without a medical background are using this resource they will likely need to consult with a medical professional before knowing how to proceed based on the list of possible diagnoses generated by the HPO. Additionally, the HPO list does not include every possible diagnosis, which is important to keep in mind when considering a differential diagnosis.

ClinGen: https://clinicalgenome.org/

ClinGen is a National Institutes of Health (NIH)-funded initiative dedicated to building a central resource that defines the clinical relevance of genes and variants for use in precision

medicine and research. ClinGen has different working groups that focus on generating and maintaining the numerous resources, tools, and registries that are linked through the ClinGen website. The registries associated with ClinGen (such as GenomeConnect, described previously) share genomic and phenotypic data in a centralized database for research and clinical use. ClinGen aims to standardize how variants are interpreted, implement evidence-based guidelines and develop algorithms for variant interpretation. The centralized databases will also improve our understanding of variants in diverse populations, determine the clinical validity of variants, and give an indication based on expert opinion of whether or not the information will alter clinical management of patients. The content and functionality of ClinGen were designed to be used by scientists and clinicians, and individuals and families may benefit more from ClinGen by bringing it up for discussion with their providers, rather than utilizing it on their own.

ClinVar: https://www.ncbi.nlm.nih.gov/clinvar/

ClinVar is a NIH-funded project that is partnered with ClinGen. ClinVar is a database that archives information on genomic variants and reports on their interaction with human health. Clinical laboratories, expert panels, professional societies, and researchers submit variants to ClinVar and rate each one on a scale of benign to pathogenic based on their own observations and ranking system. ClinGen uses ClinVar as a source of variant data. ClinGen expert panels review the variant data and submit standardized interpretations to ClinVar that provide estimates of pathogenicity that also indicate a confidence level for the call. ClinVar provides a conflict report of any differences in interpretation between their submitted variants and those already in the database. ClinVar thus facilitates communication about the relationships reported between genomic variation and observed health status/pathogenicity. ClinVar is free to the public. If an individual has a variant identified by genetic testing, they can search for the variant in ClinVar. If the variant is there, individuals can read more about its interpretation. ClinVar is a

resource individuals can consult when trying to determine the pathogenicity of a variant, however, the user must be able to understand the ranking system for both the variant and the levels of evidence. In addition, ClinVar can be confusing to use because sometimes there are multiple pages for the same variant; the nomenclature must be exact, so there is no room for error when entering the variant you are searching for.

Patient Advocacy Organizations

SWAN: http://swanusa.org/

Syndromes Without A Name (SWAN) is an organization that offers support to affected individuals and their families who have yet to receive a diagnosis. SWAN advocates for changes in the medical community that will support individuals who are undiagnosed. This is a critical resource and initiative because those who are undiagnosed often lack appropriate treatment options. This subset of people who remain undiagnosed do receive research dollars that might help them develop better therapies or management guidelines. SWAN provides great resources for families who are in this position, as well as travel grants that allow them to participate in research or testing opportunities they may not be able to afford otherwise. While SWAN is not targeted to the N-of-1 community, it still is a resource that families may find useful and easy to understand.

GlobalGenes: https://globalgenes.org/

GlobalGenes is a non-profit rare disease patient advocacy and support organization that was started in 2009. GlobalGenes aims to reduce the challenges of rare diseases for people around the world by giving the rare disease community a unified voice. They provide resources to help educate and create awareness of rare diseases. Their resources are designed to empower rare disease patients and their families to become self-advocates. Over 500 global

organizations are affiliated with GlobalGenes. GlobalGenes provides toolkits for families that cover a wide variety of topics, from how parents can advocate for their children with a rare disease in the school system to a toolkit specifically for people who have not yet been diagnosed. The organization also provides webinars, documentaries, information on drug development, fundraising campaigns, and a patient impact grants. The information provided that promote self-advocacy is especially important and useful because it applies to all rare diseases. GlobalGenes does not have information that is specifically targeted at N-of-1 rare diseases and thus does not specifically address the very unique challenges that these individuals and their families face.

Other

Google Alerts: https://www.google.com/alerts

Google Alerts is a notification service that provides alerts whenever a given topic is mentioned on the internet. The goals is to keep its users informed on new material as it is published. Google Alerts allows users to create searches for any keyword(s), tailor the results based on the source of the publication, and indicate how filtered the results will be. Google Alerts searches through blogs, news outlets, websites, videos, books, and forums. Users can modify their alerts to search through one publication source, or a combination of multiple sources. Alternatively, users can choose "Automatic" which allows Google to curate results based on what they think is most relevant to their needs. Results can also be filtered based on region of publication, language, and frequency of alerts.

Google Alerts can be utilized by anyone, and is particularly useful for N-of-1 families. Having a family member affected by a rare disease can be burdensome, and taking the time to search the internet for useful or relevant resources is not always realistic. Google Alerts

eliminates the time individuals and their families would have spent sifting through news stories, trying to stay up to date on new developments. While Google Alerts can be very useful, users can quickly become overrun with excess information and an overwhelming number of emails. Modifying the search options is critical. To avoid this, the frequency and quality of alerts should be set to ensure that emails are being received in manageable intervals, and that they contain only the best results. Unique identifiers related to an individual's disease are encouraged as keywords when curating one's search options. This could include genetic testing results (either the gene or the gene and variant) or distinctive symptoms. Ultimately, Google Alerts is only as useful as the information available, and the effort put forth by the user.

Discussion

Limitations

We created and designed our website to be both a user-friendly and comprehensive resource that N-of-1 families can utilize. We recognize, however, there are many limitations to this process and to our final product. There is a lack of research on the specific needs of N-of-1 families and, without further evaluation, we cannot be confident that we have addressed those needs sufficiently. Our survey of genetic healthcare professionals specifically asked for constructive criticism regarding specific changes each respondent would make to the website. These survey questions were not formatted in a way that would give a balanced representation of the utility of the website. Until we receive feedback and evaluations from N-of-1 families, we are not able to accurately assess its helpfulness and overall utility.

Currently, we are not affiliated with bigger rare disease advocacy organizations that could increase traffic to the website, as well as build a reputation as a legitimate resource. At present, we have no personal contact with the N-of-1 patient population, hindering our ability

to promote our resource with this population directly. As four graduate students in genetics, we also lack a lot of expertise in web design and other related aspects, such as search engine optimization. A final limitation of our website is that it only caters to English speaking families, as do most of the resources we link to and promote.

Themes Found in Survey Responses

Based on feedback from our survey questions, we identified five common themes. The primary themes these surveys were coded for were the website's aesthetic, language used, resource choices, how-to guide utility, and the clinical utility of the website as a whole. We took the qualitative responses and coded them into quantitative figures for each of these themes every time they were mentioned. For example, anytime a respondent mentioned font size, organization, layout, text density, and graphics their response was coded as an "aesthetic" theme. When respondents commented on word choice that was either too sophisticated for the target audience, or there was grammatical suggestions, it was coded as "language." When respondents suggested adding, removing, or editing current resources linked on the website, their response was coded "resource choice." Respondents were asked to comment on the how-to guides' ease of use and whether they felt they were helpful in describing each resource: these were coded as "how-to guide utility." Lastly, clinical utility was coded every time a respondent stated they would recommend this resource to a patient and their family.

From these codes aesthetics and language were mentioned the most. Edits made based on these comments included decreasing text density, increasing font size, and simplifying language like medical terminology used in the case example case story. We also adjusted the content of the website based on the feedback coded as resource choice and utility of how-to guides. We added NORD and Genetic Alliance as additional resources, and altered the

descriptions of PubMed and ClinVar. Any feasible comments were incorporated, while others were disregarded based on limitations set by the website building platform of Squarespace (i.e. banner size, menu header font size, layout, and adding a discussion forum). All of the survey participants responded favourably to the utility of the website as a whole. When asked if the resource was one they would use in the future, or recommend to patients and families, all of them responded, “Yes”.

Future Directions

Now that the website and how-to guides have been developed they need to be evaluated for utility and ease of use. The website needs to be tested by N-of-1 families to ensure that the content is appropriate and accessible for the general population. The how-to guides will need to be revised in the future as the primary resources are updated. Additionally, new how-to guides will need to be developed as more resources and technologies, such as new matchmaker databases, are created for the rare disease community. We would like to eventually feature stories of N-of-1 families on our website to both enhance our connection with the target audience, and create online discussion forums on our website so that families can interact with others facing similar situations.

Additionally, we need to bring awareness to our website. We plan to contact different rare disease advocacy organizations in the hopes of partnership and mutual promotion of each other's resources. In addition to these essential advocacy connections, serious efforts need to be made in order to promote and advertise this resource. By attending genetics-focused conferences in the future, we will be able to promote our website to genetics professionals so that they can provide this resource to N-of-1 families at the time of diagnosis.

This project will continue to evolve to fulfill its full potential and its ultimate goal. We as a group are excited about DNA Unicorn and its potential to help N-of-1 families.

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Appendix A

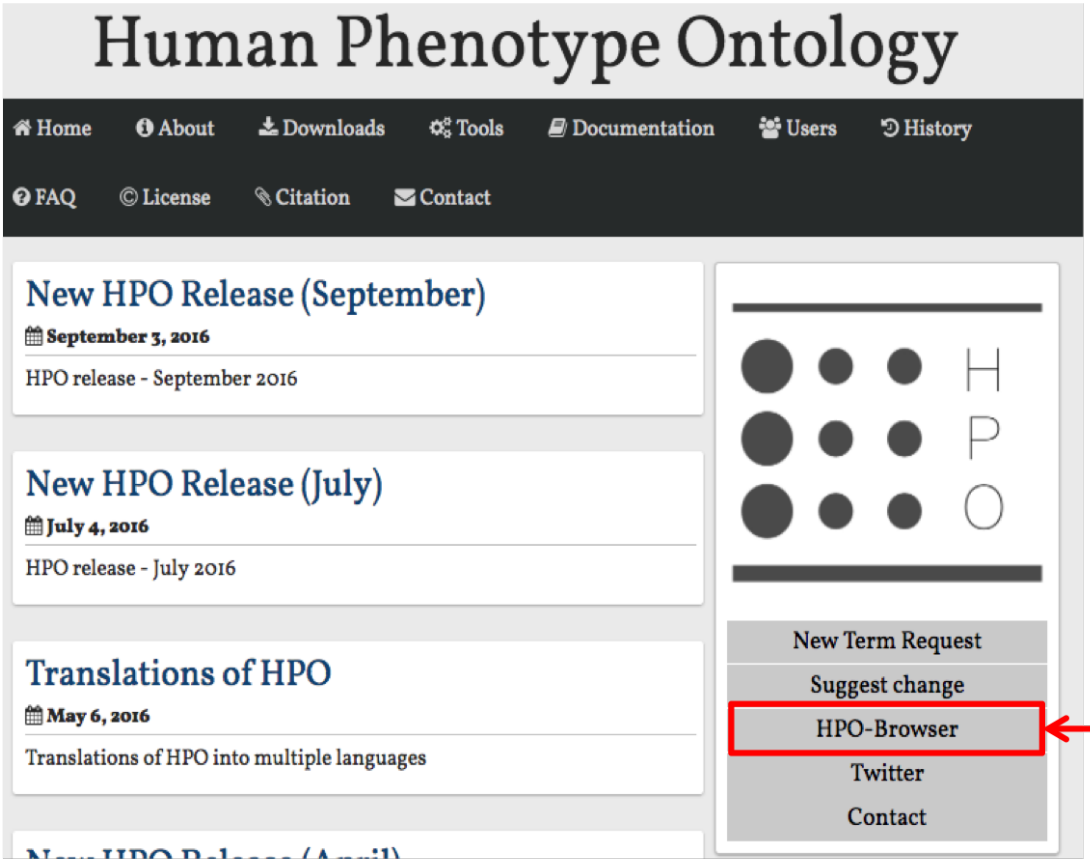
Formatting slightly different on website.

Human Phenotype Ontology Guide

PART I: The HPO

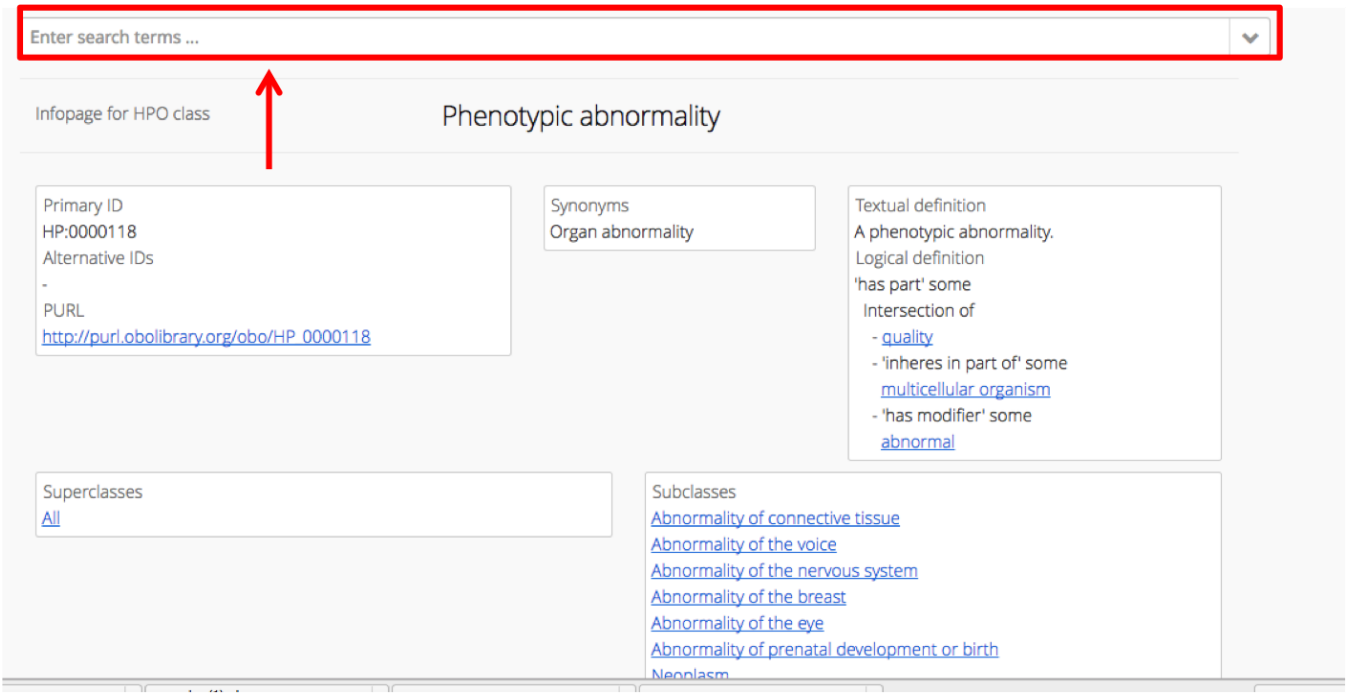
One resource that you may find useful is the Human Phenotype Ontology or HPO. The name alone sounds a bit daunting doesn't it? The Human Phenotype Ontology is a database that is trying to help standardize the medical terms used to describe different phenotypes (an individual's traits/characteristics/symptoms) associated with human diseases. This resource is very helpful for scientists and clinicians, but may also be helpful for you. Admittedly, it isn't the most user-friendly but hopefully this guide will help you if you are interested in giving it a try. The HPO can help you in figuring out the medical terms that are used to describe the features associated with your or your loved one's disease. Knowing the correct medical terminology can help you search for others by using these terms and can also help others to find you.

To get to the HPO homepage go to http://human-phenotype-ontology.github.io/. The HPO homepage is pretty busy and most of it will not be useful to you. There are many different tools and other databases that use the HPO that you may come across if you explore the HPO website. Most of these were designed for researchers and are really only useful for that purpose. To get to where you can search the HPO go to lower right of the homepage.

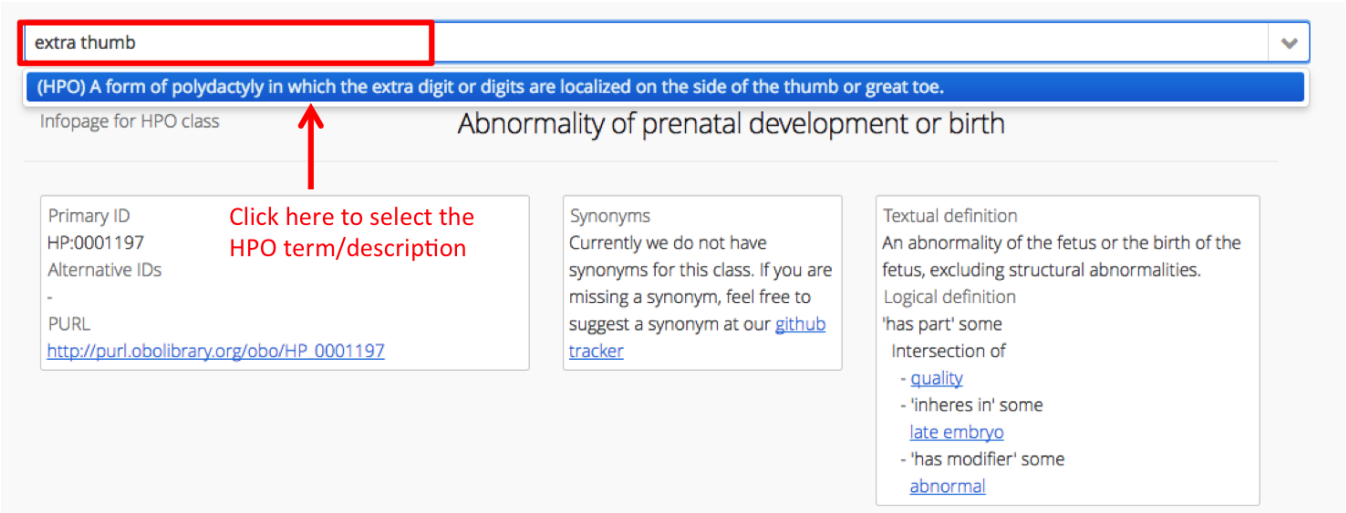


To get to the HPO search function, go to the HPO homepage and click on HPO-Browser. The URL on the browser changes with each update, so it is better to bookmark the home page and go through here each time.

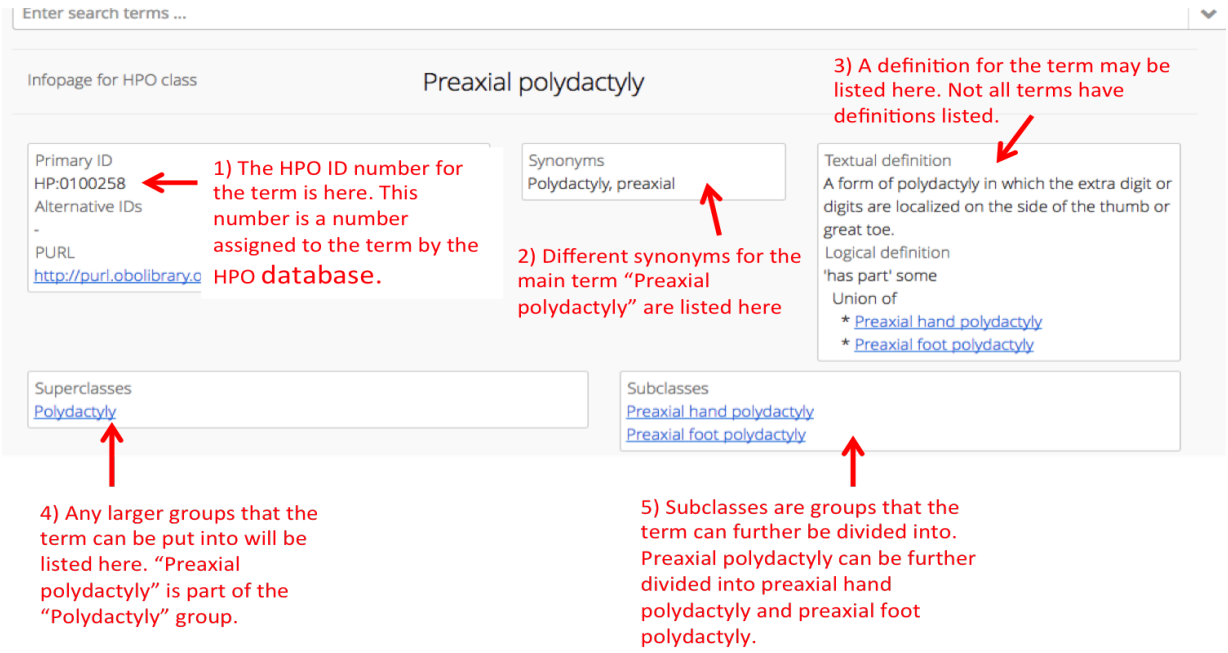
After clicking on the HPO Browser button you are taken to this page where you can search the HPO. You can type in the words that you would use to describe the features of your or your child's genetic disease.



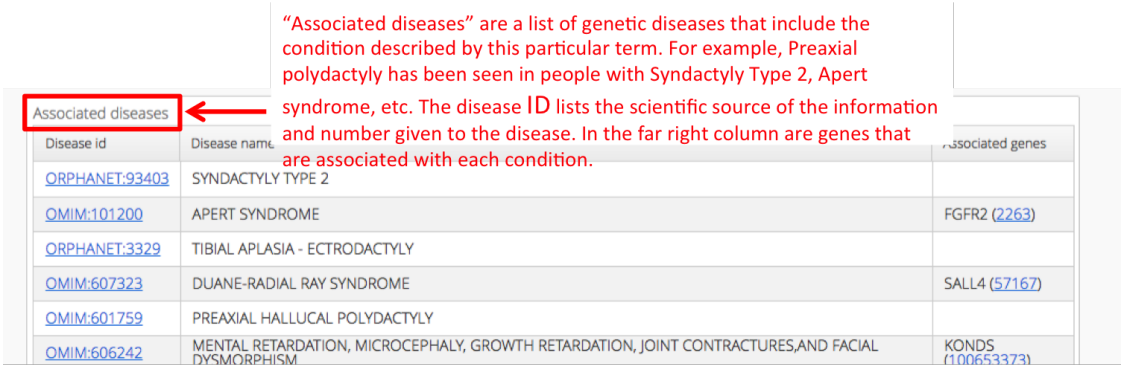
We will use the example of Anna (see our mock patient story first for the full description of Anna) to explain how to use the HPO web browser. One unusual feature of Anna's condition is an extra thumb. If you type extra thumb into the search bar, the medical terms and/or descriptions in the HPO database that match it will pop up in blue below. In this case there was only one option because the words used to search were pretty specific, but sometimes multiple options will pop up depending on what you entered. We will click on the blue box to select the HPO term/description to continue.

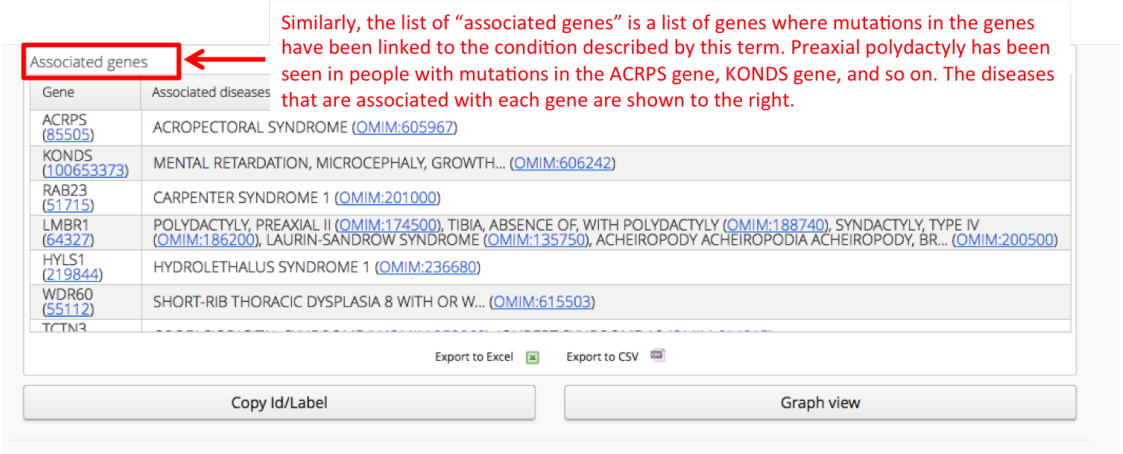


After selecting a term/description from the list of options in the blue drop down menu you will be taken to that term's page. Using our example of extra thumb, we selected the only option that appeared in the blue drop down menu. In doing this we are taken to the page for "Preaxial Polydactyly".

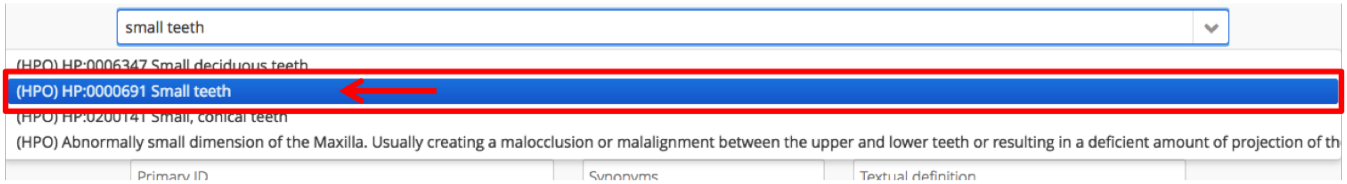


Scrolling down the page you will see several different boxes, each with different information

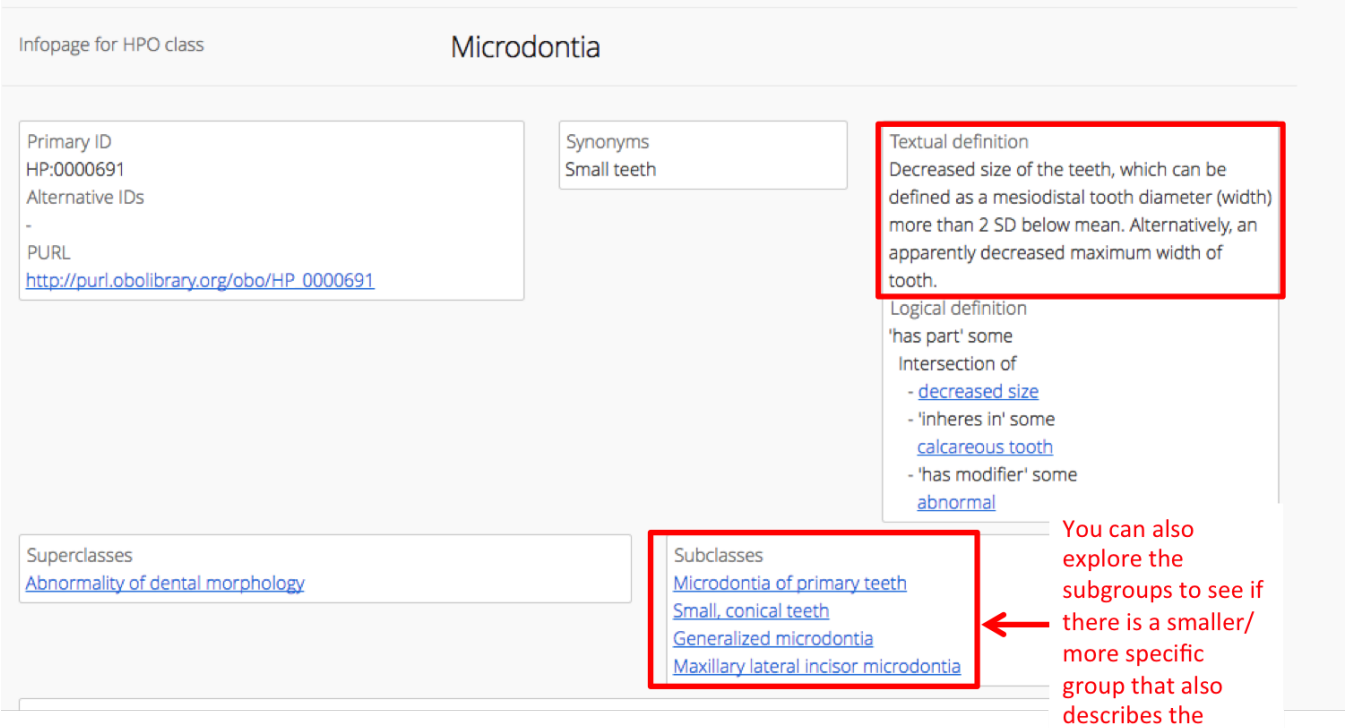




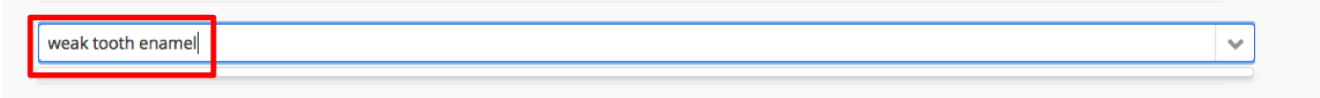
Let's do another sample search. Anna was described as having small teeth. When you type small teeth into the search bar, several matching options appear in the drop down list. We selected the "Small teeth" option from the list first because it was exactly what we typed in and was the simplest term/description listed. It may be easiest to always start with the simplest term first. You could always select one of the other options and explore the page for that term to see if it fits with what you are trying to describe. If it doesn't fit, you can always go back and choose another term from those in the list.



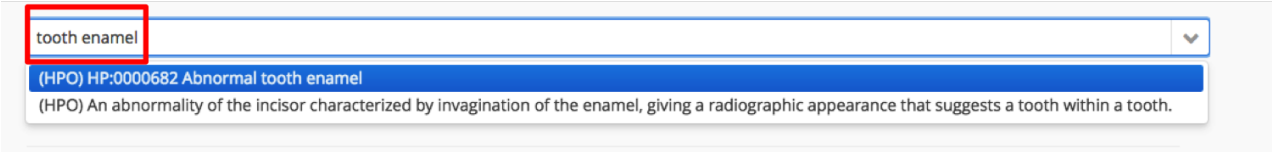
Clicking on the "Small teeth" option takes us to the page for Microdontia. The definition fits with our description of Anna. If it didn't seem to fit we would go back and select a different term from the list.



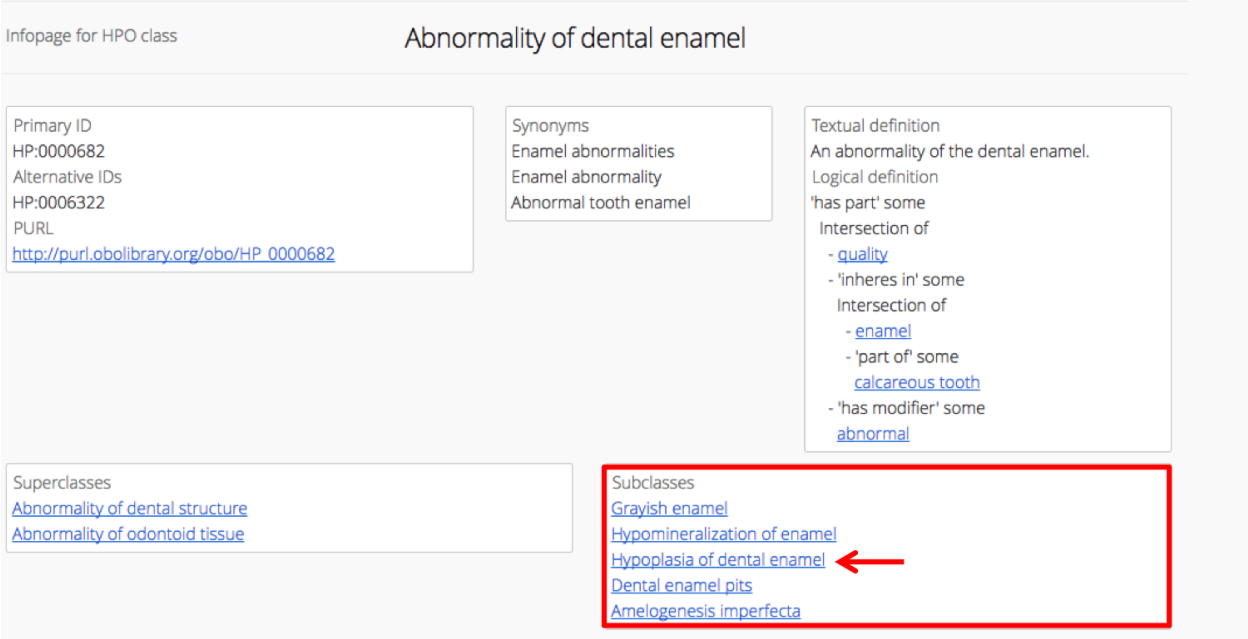
We will do one final example using Anna's story. Sometimes you will type in a term and no options will appear. This means that what was typed in the search bar hasn't been linked to an HPO term yet. If this happens you could try using a different description or searching for a broader term first.



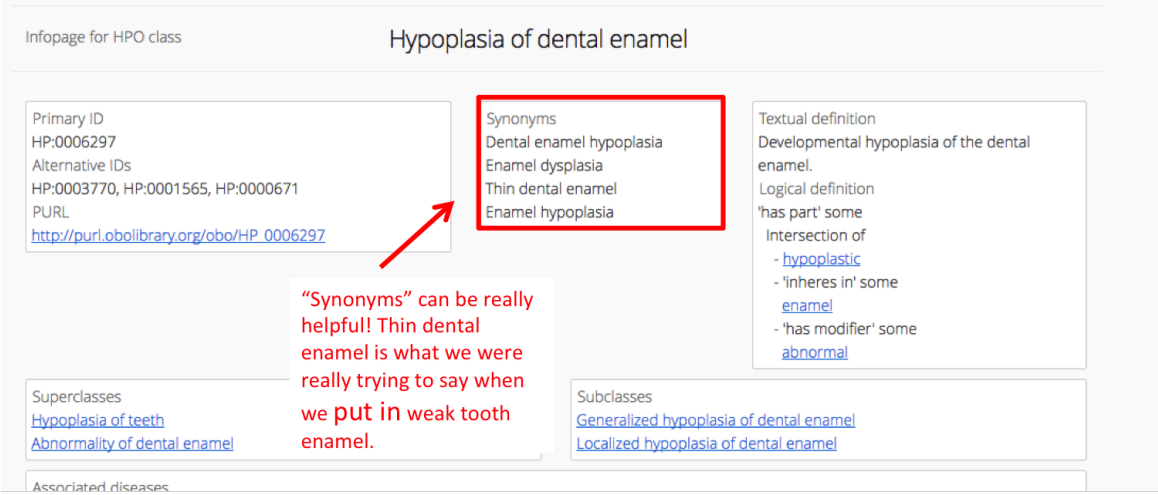
When we removed the word “weak” and kept “tooth enamel” options appeared in the drop down list. We selected Abnormal tooth enamel.



“Abnormality of dental enamel” fits with what we are trying to describe (weak enamel) about Anna, but is still a pretty broad term. If the term you end up with seems too broad you can look for more specific terms by looking at the terms listed under “Subclasses”. You can explore the different subclasses of terms on HPO using Google. In this case, the term “Hypoplasia of dental enamel” seems to fit best.



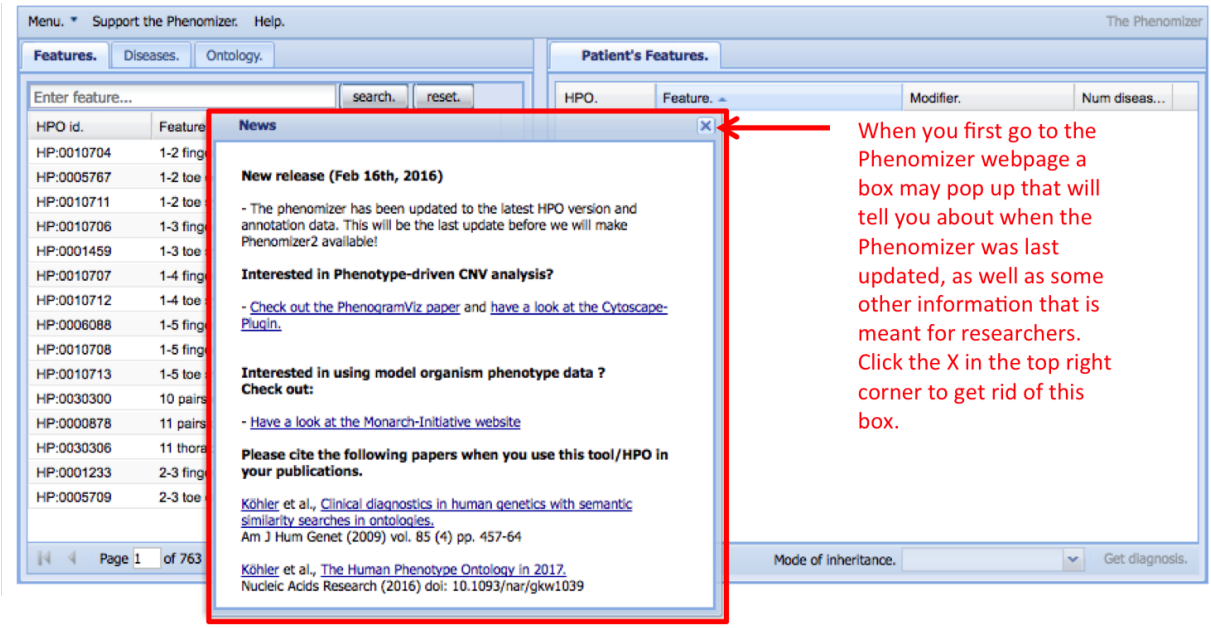
The page for dental enamel hypoplasia doesn’t have a very helpful definition so we had to Google dental enamel hypoplasia to get a better understanding. The “Synonyms” are helpful, so remember to look for those when you are trying to understand the definition of a term.



Now you are ready to get started using the HPO! It can feel a bit like trial and error when using it, especially at first, but it does get easier the more you play around with it. If you are feeling comfortable with the HPO then check out the Phenomizer (see below), which is a database that uses the HPO terms.

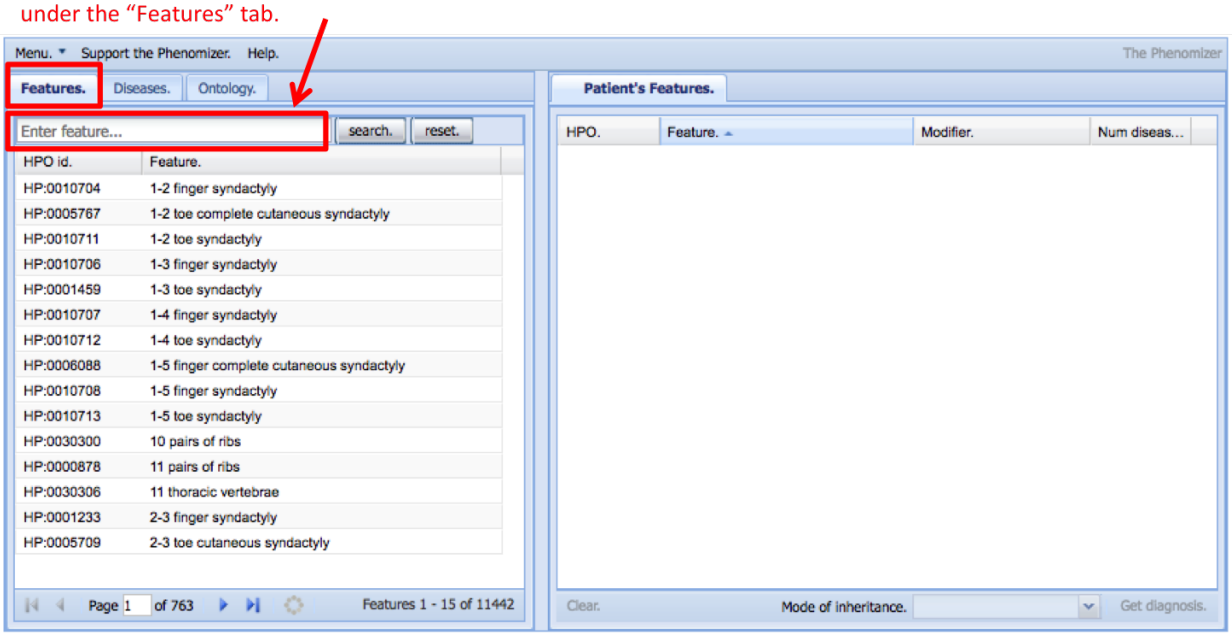
PART II: The Phenomizer

The Phenomizer is a tool where you can enter the features, signs, and symptoms (the phenotype) of the affected person in your family to see if there are known diseases that match with their condition. The Phenomizer was designed for physicians to use to help in diagnosis, but is open to anyone. That being said, it is not the easiest tool to navigate, and like the HPO it can take some time to get the hang of it. To access the Phenomizer go to https://compbio.charite.de/phenomizer/.

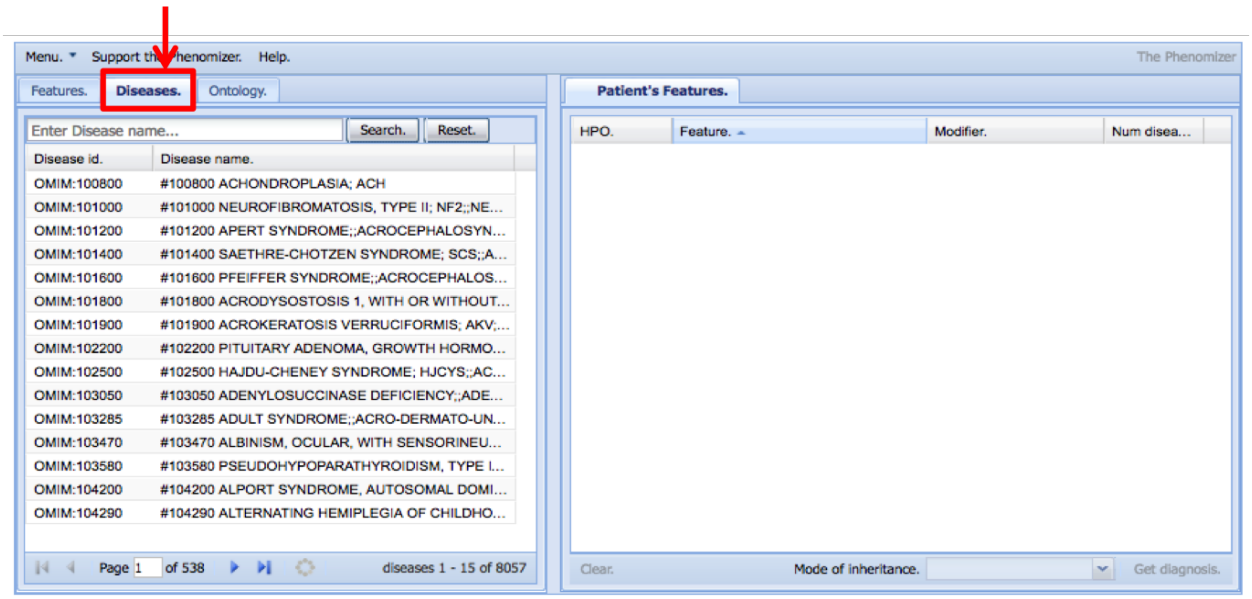


Phenomizer uses the HPO database medical terms and applies these to the diseases that are in the Phenomizer database. It is easiest if you have already used the HPO to create a list of the medical terms that apply to the features and symptoms of the affected person. You can sometimes search the Phenomizer using non-HPO words to describe the disease. The HPO terms will sometimes pop up, but not always, so it's easiest if you already have them handy. See the first part of this guide for tips on how to find the HPO terms.

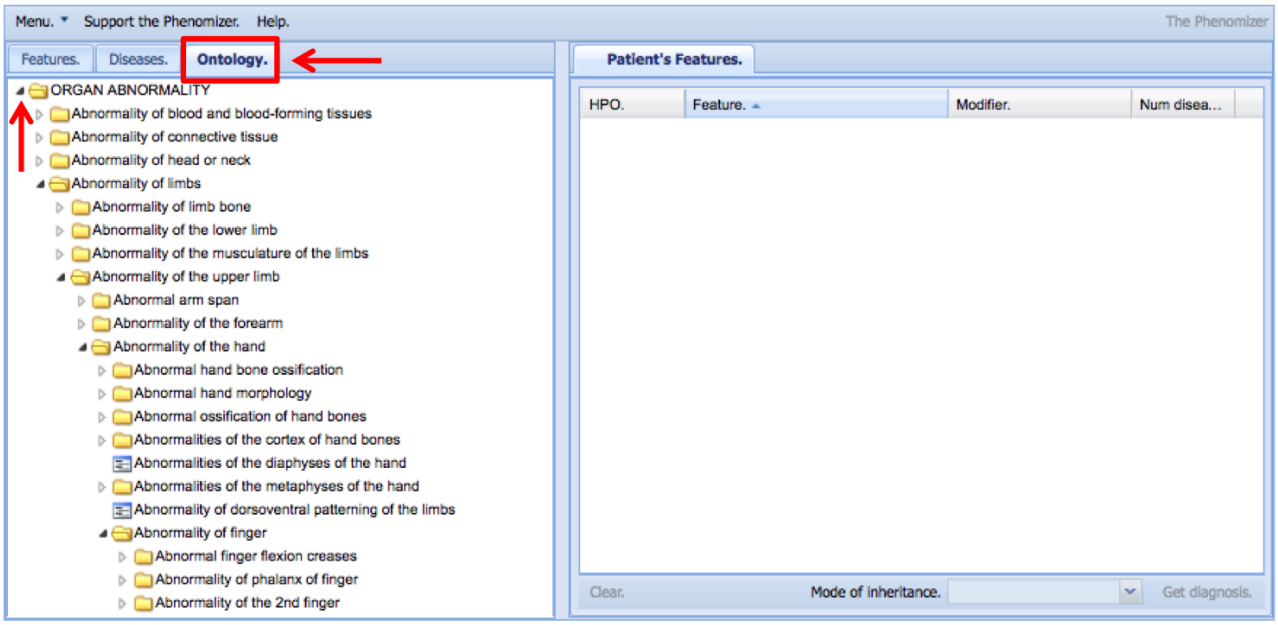
Once you have all of the HPO terms that describe the affected individuals symptoms and features you can enter them individually into the “Enter feature” bar under the “Features” tab.



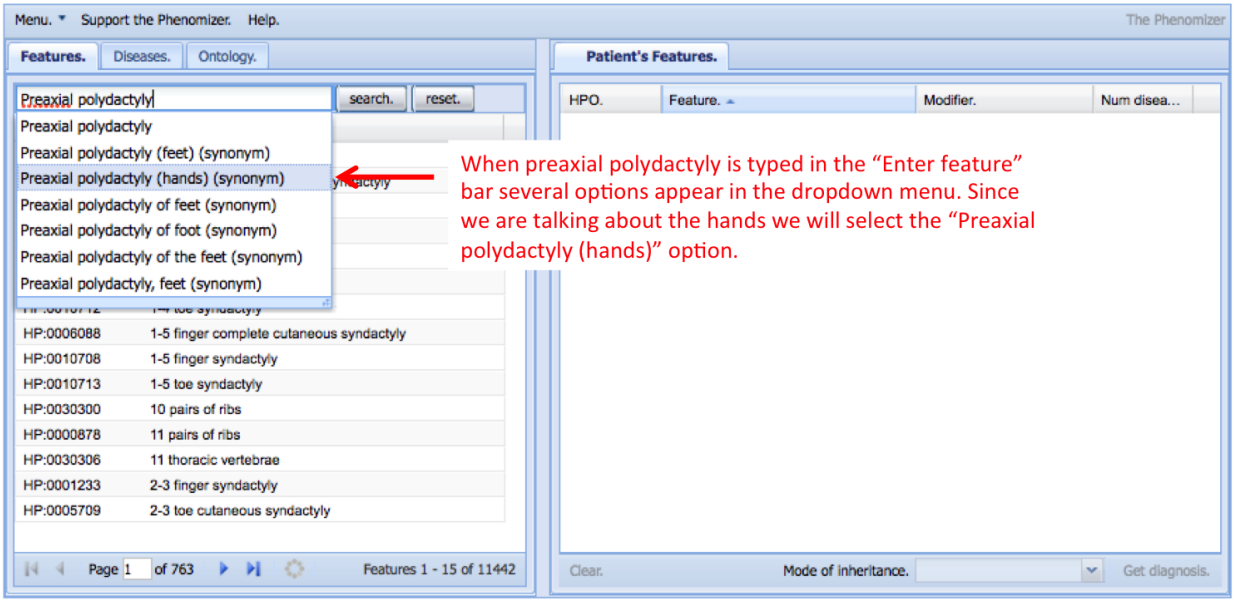
You can also search the Phenomizer database by disease name under the “Diseases” tab if you have the name of a specific disease and want to see if that disease is in the Phenomizer database.



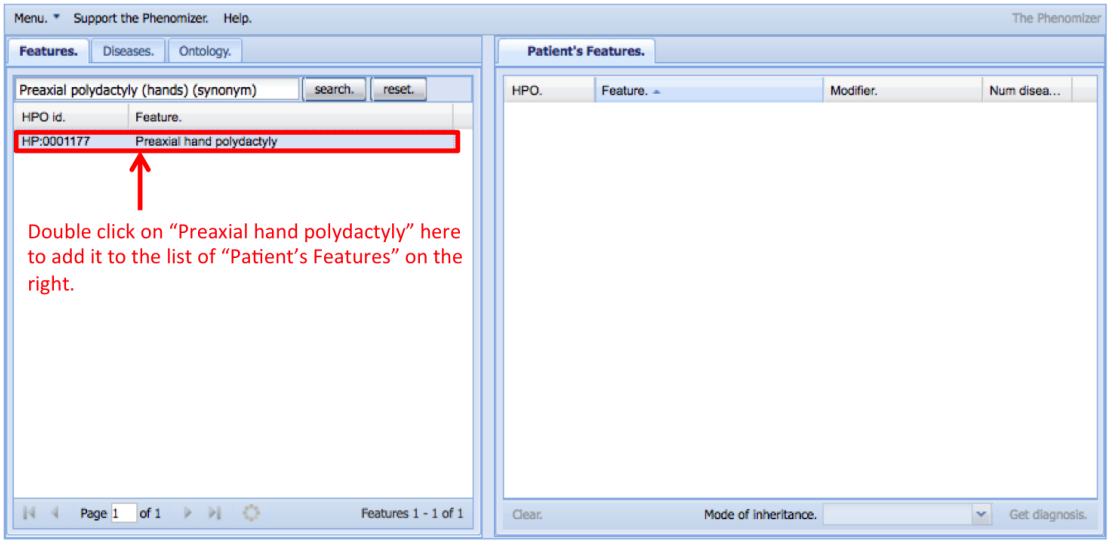
If you aren’t sure of the medical/HPO term to describe a symptom you can try to find it under the “Ontology” tab. This tab has one main folder “ORGAN ABNORMALITY” and many subfolders within the main folder. If you click on the small arrow next to the main folder it will show you the subfolders, and the same for each subfolder. The folders are divided by organ systems so you can search through the folders until you have a term that describes the symptom you are trying to describe. This can be very time consuming so it’s recommended that you try to find the medical terms via the HPO first.



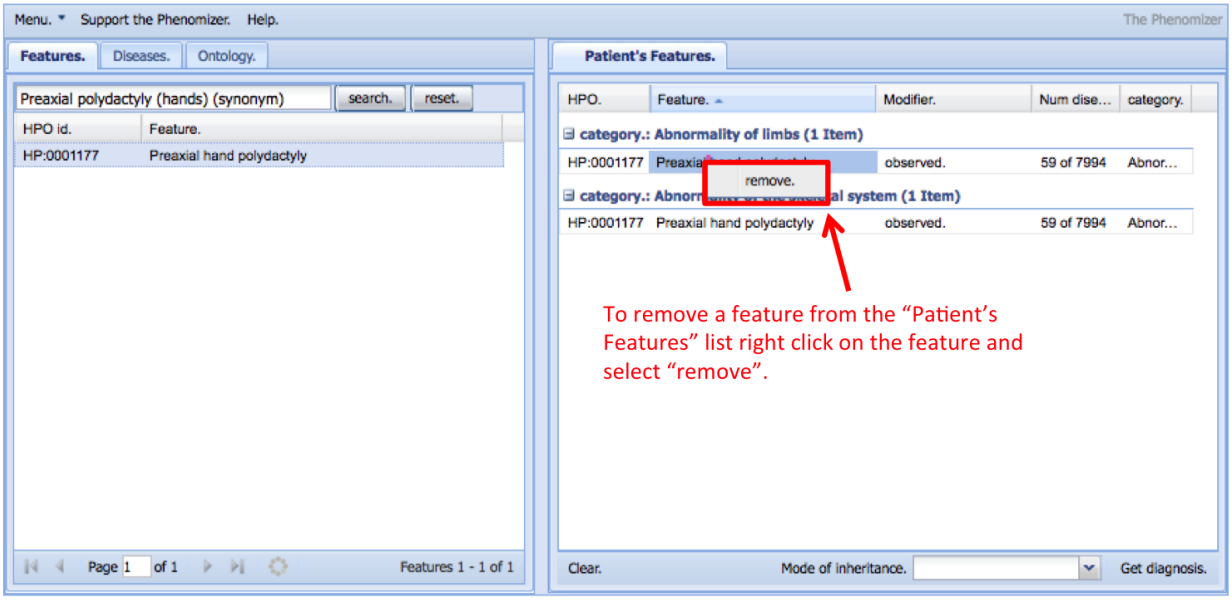
We will again use the mock patient Anna to demonstrate how to use the Phenomizer. We will enter all of Anna's symptoms and unique features into the Phenomizer, one at a time. One of the features Anna is described as having is extra thumbs, which we now know is called "preaxial polydactly" from searching the HPO (see Part 1 of this guide). We will enter "preaxial polydactyly" into the "Enter feature" bar under the "Features" tab.



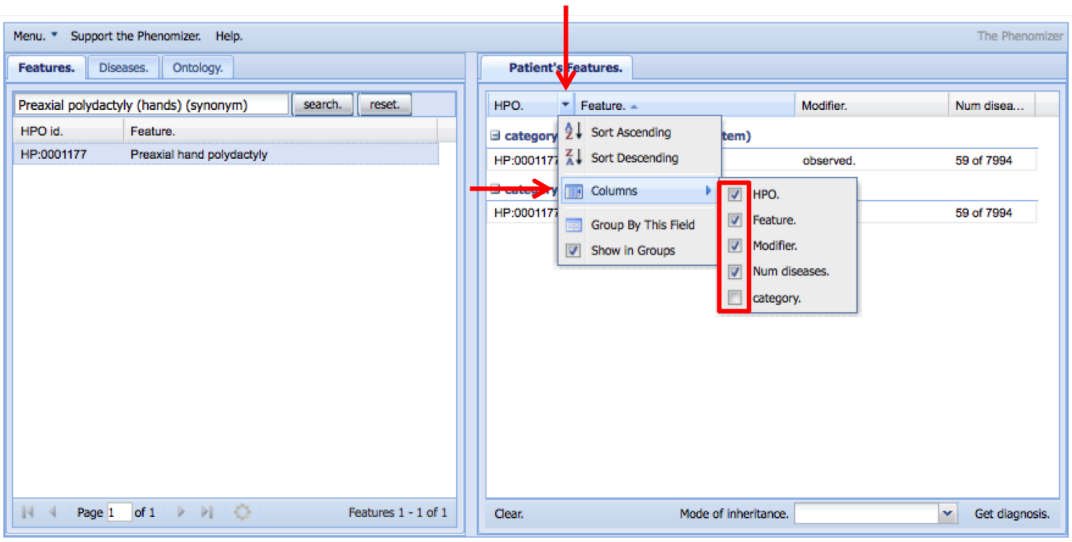
We have now selected "Preaxial hand polydactyly. To the right of the screen will be a list of all of the patient features once you add them. To add a feature to the list on the right you have to double click the feature on the left.



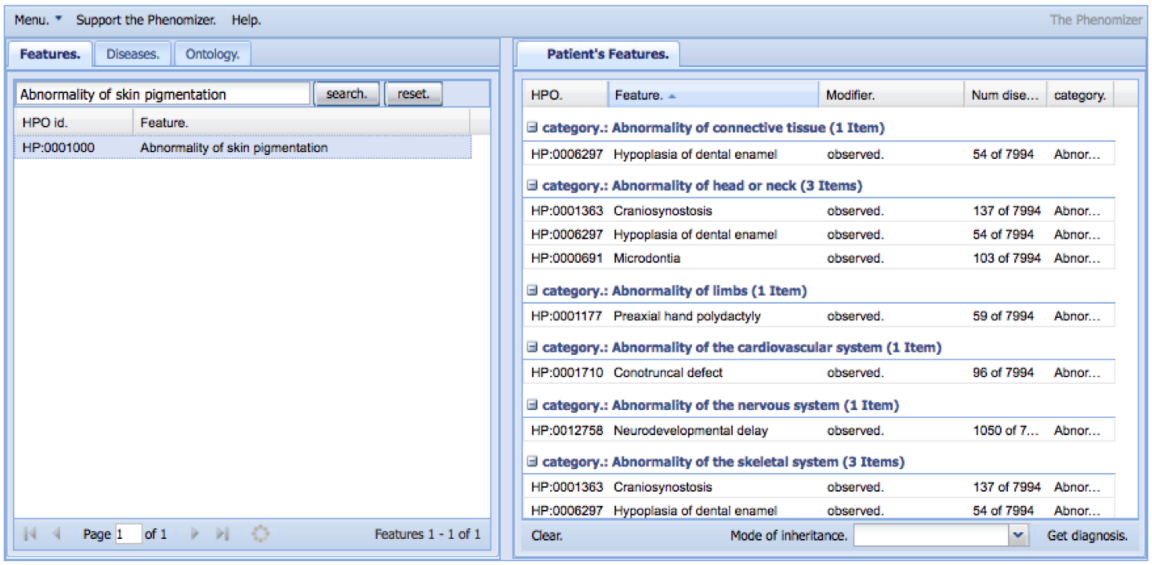
When you add a feature to the Patient's Features list the feature may appear in the list under different categories. Any broader category the feature can fit in will appear in the list. For example, Preaxial hand polydactyly can fit into the categories "Abnormality of limbs" and "Abnormality of the skeletal system", thus both appear in the list.



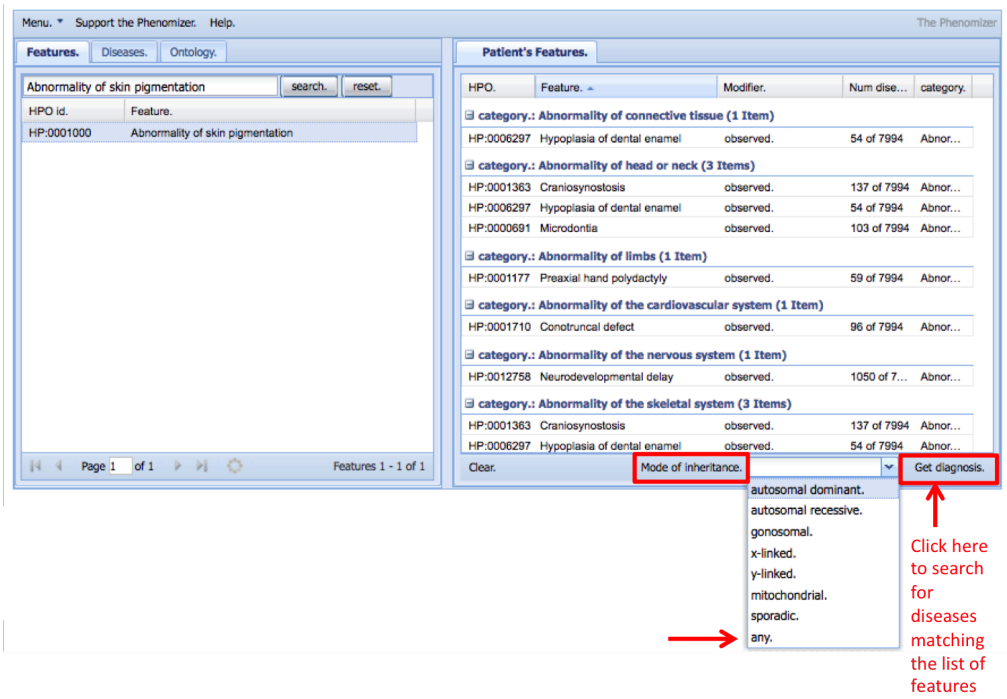
There are five different possible columns under the Patient's Features list and you can select which ones you would like to view or hide. To select which columns you would like to view click on the arrow next to "HPO", select "Columns", and add a checkmark next to the option to view it or remove the checkmark if you don't want to see that column. The "Feature" column lists each feature added to the Patient's Features list. The "HPO" column lists the HPO ID number for each feature. The "Num diseases" category lists how many diseases in the Phenomizer database include this feature.



You can continue adding features by typing them into the “Enter feature” bar on the left and double clicking on the feature. We have added all of Anna’s features and symptoms to the Patient’s features list.



Once you have added all of the symptoms/features to the Patient’s features list you can select the type of genetic inheritance pattern you want to search for when searching for diseases. If you know how the genetic mutation in the affected individual was inherited you can select the specific pattern; otherwise, select “any”. When you are ready to search for diseases that fit with the list of features click on “Get diagnosis” at the bottom right of the page.



A list of possible disease will appear under the “Diseases” tab. The diseases that most closely match the list of features will be located at the top of the list. The “p-value” is a word used in statistics, and the lower the p-value the more the disease fits with the list of features. In statistics if a “p-value” is less than 0.05 this is considered statistically significant -- meaning that there is a high likelihood that the association between the two things did not happen by chance. In our example the p-values are all a lot higher than 0.05, meaning there isn’t a significant relationship and that the diseases listed don’t match well with the list of Patient’s features. You can always explore some of the diseases by using Google to search for them. Now you have the basics on how to use both the HPO and the Phenomizer. For more in depth information on the Phenomizer, download the user manual under the “Help” tab. Good luck!