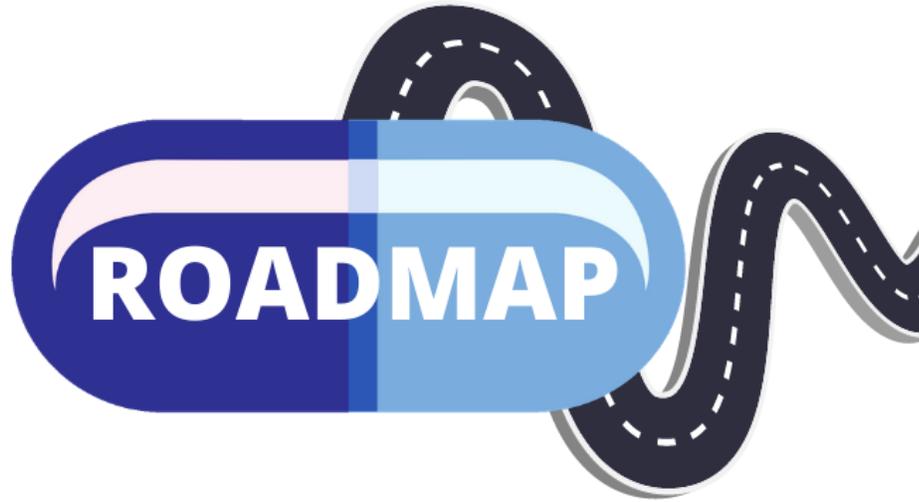


# The ROADMAP Project



Conducted by the Castleman Disease Collaborative Network

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# The ROADMAP Tool: Repurposing Stages, Roadblocks & Insights

The ROADMAP tool is the culmination of the Repurposing Of All Drugs, Mapping All Paths (ROADMAP) project, pursued by the Castleman Disease Collaborative Network (CDCN). The CDCN identified as many rare disease nonprofit organizations and potential stakeholders as possible, distributed a survey to these stakeholders, and performed in-depth interviews with a subgroup of representative stakeholders. Then, we utilized this information along with our experiences from rare disease drug repurposing to build out the ROADMAP tool.

Based on our experiences with drug repurposing, 605 survey responses which made inclusion criteria from rare disease stakeholders, and 25 in-depth interviews, we have organized the drug repurposing process into 5 steps:

1. Supporting repurposing
2. Identifying the drug
3. Validating the drug
4. Utilizing the drug clinically
5. Reaching an endpoint

You can explore the tool and its contents by clicking the circles on the main line in the tool to the left, as well as each of its subcategories.

**“Supporting repurposing”** involves laying the groundwork to be able to successfully repurpose a treatment for your rare disease. This may involve setting up a rare disease non profit, creating the vital research infrastructure, fundraising or applying for grants that you can then provide to researchers, creating a contact registry of all your patients, creating a network of researchers and physicians who are already or potentially could be doing work related to your rare disease, and/or developing certain resources, such as a [biobank](#) or a [natural history study/registry](#).

**“Identifying the drug”** describes the next step in the repurposing process. It entails identifying existing drug(s) that may be potentially beneficial for your patient population of interest. There are many ways this can be done (high throughput drug screens, machine learning data mining, analysis of real world off-label drug use, etc.), which we explore in detail in the ROADMAP.

**“Validating the drug”** explains the important step in which the initial hypothesis about the potential of the identified drug(s) is tested in the laboratory or through other research approaches. This step is sometimes skipped.

**“Utilizing the drug clinically”** - if the drug seems promising enough for the anticipated benefits to outweigh the anticipated risks, it can move on to being used in patients, either in an official clinical trial or through an “off-label” prescription by a physician.

**“Reaching an outcome”** refers to the final step in the drug repurposing process. Once the drug has been given to patients, it should be evaluated to determine if it is effective and which patients should receive it. Though

FDA-approval for the new disease is often thought of as success, many drugs are never reviewed by the FDA and there are several potential positive outcomes of drug repurposing, such as inclusion of the drug in treatment guidelines and off-label use of the drug in patients that improves quality of life. Failure is defined as the drug being abandoned due to issues with safety or efficacy, whether or not it is approved by the FDA for this new use.

Throughout all of these steps, there are many ways that rare disease non profit organizations can play a supportive role or some aspects of the drug repurposing process, which we detail throughout the tool.

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## 1. ENABLING REPURPOSING

Among the stakeholders involved in the drug repurposing process, rare disease nonprofit organizations are a powerful intermediary between the patients, researchers, physicians, regulatory agencies, pharmaceutical companies and other actors. Their power lies in leveraging their personal passion and perseverance against all odds to help patients and create and foster the right ecosystem to drive forward drug repurposing efforts for their rare disease(s).

The ways that a rare disease organization can support drug repurposing projects fall into four somewhat overlapping categories:

- **Funding Support**
- **Research Support**
- **Partnering & Collaboration Support**
- **Patient Support**

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### FUNDING SUPPORT

Drug repurposing projects require financial resources. In order to support these projects, a rare disease nonprofit serves two intertwined functions, as a fundraising entity and as a fund-allocating entity.

#### ***FUNDRAISING***

There are many ways an organization can raise money. One way to think about this is to focus on different entities that can contribute funds:

1. Patients & their families
2. Individual large donors
3. Government organizations
4. Other nonprofit organizations

#### ***FUND-ALLOCATING***

Once the funds are raised, there are a number of initiatives that a rare disease nonprofit can contribute funding to that can help to facilitate drug repurposing:

- Research-related activities\*
  - Basic research studies
  - Preclinical/translational research
  - Other drug repurposing candidate identification approaches (e.g., high throughput drug screens, etc.)
  - Resource development (animal models, cell lines, biobanks, registries, etc.)
  - Clinical trials
- Community-focused activities
  - Collaborations between different rare disease organizations (pooling resources for either research, patient support, events, etc.)
  - Grants to early career researchers to help grow researcher network
  - Creation of research consortiums and meetings/events
  - Supporting patient drug access
  - Supporting a patient discussion platform
- Patient care-centered activities
  - Establishment of expert panels to create treatment guidelines
  - Creation and work of centers of excellence
  - Genetic screening

\*The details will be explored in more detail in the [“Research support”](#) section.

It is also important to note that there are different approaches to how a nonprofit organization can select which research and researchers to fund.

- The traditional approach involves an organization announcing a request for proposals (RFP) that invites researchers to submit a research proposal (a research question, approach to answering the question, and budget) that addresses the question or area of research described in the RFP. The organization then reviews and awards funds to the best proposal(s).
- An alternative to the researcher-centric model is the “Collaborative Network Approach” (16). It consists of eight steps and leverages and integrates the entire community of stakeholders — patients, loved ones, physicians and researchers — to identify and prioritize high-impact research questions. One of the most important steps of this approach is a crowdsourcing process, which “allows the entire community to identify the most clinically relevant and pressing questions; any idea can be translated into a study rather than limiting research to the ideas proposed by researchers in grant applications”. Read more about the Collaborative Network Approach at <https://cdc.org/about-us/our-approach>.

Regardless of the amount raised or grant allocation approach, rare disease organizations can start to create a “seed” funding budget for research projects which either directly or indirectly relate to drug repurposing. Even if these are small grants that may not be enough to complete large-scale projects, these small grants can enable the first proof-of-concept studies to take place, enabling the researchers to then apply for larger grants from entities like the FDA, NIH, etc.

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## RESEARCH SUPPORT



Drug repurposing is primarily a research process in order to identify and validate treatments for diseases, which have not been tried before. Nearly all (86%) of the rare disease nonprofit organizations that completed the ROADMAP survey support research in their rare disease in one way or another, while 58 (40%) are supporting a drug repurposing project now, or have in the past. Many organizations split up their research funding between novel drug development (including gene therapy) and drug repurposing.

Drug repurposing for some rare diseases can provide a drug that provides full remission for at least some portion of patients, while for others it can simply be a good option to reduce symptoms, slow disease progression or improve quality of life in other ways until a more targeted drug can be developed. Drug repurposing, whether it is successful or not, also helps improve understanding of rare diseases and treatments, which can help support better and potentially faster novel drug development.

Rare disease nonprofit organizations can play several important roles in supporting various types of research related to drug repurposing by:

1. Leading the creation of patient-centered research agenda
2. Creating research infrastructure & gathering data/samples for future research
3. Providing data/samples to researchers & supporting clinical trials

### Creating a patient-centered research agenda

Though researchers may be experts in their field, a rare disease nonprofit organization can provide crucial insight based on the patient experience of having a rare disease. There are things that are important to patients, which may not be prioritized from a research perspective. For example, quality of life is more important for some populations than a marginal increase in overall survival rates; patients with chronic rare diseases may care about the effects of the rare disease or the treatments on more “everyday” things like fertility, cognitive development, as well as a decrease in overall pain or inconvenient drug delivery methods (needing to drive to a hospital to get regular treatments). This is why it is crucial that rare disease research is focused not only on filling the gaps in the literature, but also on the needs of the patient population. One example of this approach is CDCN’s [All In Movement](#), which leverages and integrates the entire community of stakeholders — patients, loved ones, physicians and researchers — to identify and prioritize high-impact research questions.

In addition to keeping the pulse of what is most important to the patient and loved one community, a rare disease nonprofit can also do extensive literature review to keep itself up to date on the latest research on its rare disease. This has a lot of potential benefits as it may:

- Create an additional value-add on the nonprofit as a potential collaborator with both academics or pharmaceutical companies
- Create opportunities to form cross-disease collaborations
- Identify new potential drugs to repurpose
- Enable the organization to learn from other nonprofits (what's already been done, what's in progress, what's planned elsewhere. You don't want to reinvent the wheel, repeat studies that have already been executed or are underway or are being planned, etc.)
- Identify researchers to collaborate with, invite to events, or to be a part of your SAB/MAB
- Learn how to model research approaches, including designs of clinical trials

## **Creating research infrastructure & gathering data**

Rare disease nonprofit organizations can help fund the development of research resources, such as cell lines, mouse models, biobanks, natural history studies and patient registries. These data and research samples can then be made available to researchers to pursue various studies, including ones that can lead to a drug being identified for repurposing. The following are examples of some of the types of infrastructure an organization can set up and maintain.

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### Patient network

One of the most foundational ways a rare disease nonprofit organization can support research is for it to act as an intermediary between the patients and the researchers/physicians. In this way, its contact registry (a database of contact information for all your rare disease patients) becomes an incredibly valuable resource. It can be used to gather data, spread the news about opportunities to participate in clinical trials, and share research findings (including new treatment options as a result of repurposing).

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### Research network

There may be dozens of researchers around the world which are already researching a specific rare disease, or doing research which is related to a potential drug target or potentially important pathway. Finding them and creating opportunities to enable them to collaborate can drastically speed up the pace of innovation and treatment identification for drug repurposing.

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### Biobank

A biobank is a storage facility for biological samples for use in research. These samples may include human tissues of any type (blood, lymph node, etc.) These samples can be included in basic research around disease mechanisms through translational research leading to treatments. Biobanks have the potential to accelerate rare disease research by providing access for researchers to high quality biological samples for their research. The operating costs of biobanks vary widely based on the scale of the

operation. Though the costs can be beyond the scope of smaller organizations, there are commercially operated biobanks which can be hired to outsource the biobanking of rare disease tissue specimens.

Among the 147 organizations surveyed in this project, 45 (31%) utilize a biobank. This includes 24 (41.38%) of the 58 organizations that are pursuing drug repurposing. Among the 5 organizations who had a drug FDA-approved through a drug repurposing project, one (16.67%) has a biobank. Having a biobank of samples can be helpful in supporting several types of research projects which may lead to identifying potentially helpful drugs for a rare disease.

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### Patient registry and Natural History Study

Patient registries are databases used to collect data (patient contact information, demographics, basic health information, medications, diagnosis, comorbidities, hospitalizations, etc.) and provide information to help researchers and clinicians understand the disease course over time.

Natural history studies are research studies that analyze data gathered in a patient registry over time. This type of study aims to gain a better understanding of the disease's natural course, including its symptoms, signs, and complications, as well as how it affects patients' lives. The information collected in a natural history study can be used to identify drugs for repurposing, and improve patient care.

There are hybrid “natural history registry” options as well, such as CDCN’s [ACCELERATE](#), in which patients self-enroll, the research team obtains medical records, and data collection is centralized and implemented into new and existing research priorities.

Among the 147 organizations surveyed, 59/147 (40%) utilize a natural history study or patient registry. This includes 52/111 (47%) of the organizations that support research and 30/58 (78%) of those that are pursuing drug repurposing. 3/5 (60%) of the organizations who have had a drug FDA approved utilize an NHR or NHS. These findings suggest that having a natural history study or registry can be helpful in supporting several types of research projects which may lead to identifying potentially helpful drugs for a rare disease.

Resources:

- [Natural History Study \(nih.gov\)](#)
- [Funding opportunities for rare disease research | FDA](#)
- [IAMRARE® Registry Program - NORD \(National Organization for Rare Disorders\) \(rarediseases.org\)](#)
- [Natural History Study \(nih.gov\)](#)

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### Tracking off-label drug use

Off-label drug use refers to the use of a drug for a disease that has not been specifically approved by regulatory authorities, such as the FDA in the US. It is quite common and is used in cases where a drug has been found to be potentially safe and effective for a new disease through research, or a physician

has reason to believe it may help a patient from their own medical knowledge or anecdotal reports from other doctors. This can be incredibly helpful for patients that are not responding to the standard of care or have no standard of care for their disease. However, off-label use of drugs can also have risks. Since the safety and effectiveness of a drug for an off-label use have not been established, there is a potential for adverse events or lack of efficacy. Tracking off-label drug use can provide information on how well the drug works in different populations or for different conditions, as preliminary data to more formal research, or in lieu of formal research. This can serve as justification to support the official integration of this treatment into treatment guidelines or help a patient gain access to a drug via letter to an insurance company, if the request for coverage was denied.

To be able to utilize off-label drug use as an avenue for drug identification, rare disease nonprofits can systematically track off-label drug use in their patient populations by implementing a few different strategies:

1. **Surveys and questionnaires:** Surveys and questionnaires can be used to gather information from patients and caregivers about their experiences with off-label drug use. These surveys can be distributed through the nonprofit's website, social media, or mailing list, and can include questions about the types of drugs being used, the reasons for off-label use, and the outcomes of treatment.
2. **Patient registries:** Registries can be used to collect and track information about patients with a specific rare disease, including information about the treatments that patients are receiving and its effects (and side effects) over time.
3. **Collaboration with healthcare providers:** Nonprofits can collaborate with healthcare providers to gather information about off-label drug use in their patient populations in order to identify trends and patterns in off-label drug use.
4. **Literature review:** Nonprofits can help identify information about off-label drug use in their patient populations by searching for articles and studies that have been published in peer-reviewed journals, and reviewing data from clinical trials and observational studies.

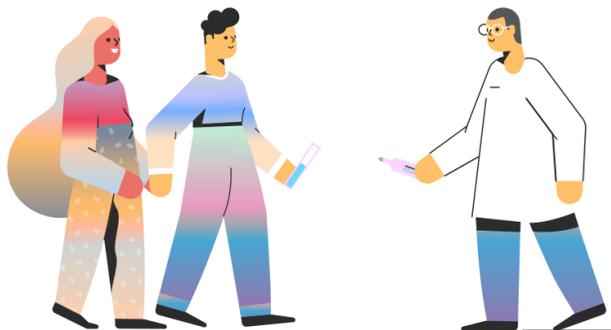
Among the 147 organizations surveyed, only 17 (12%) track off-label drug use within their patient populations. This includes 16/111 (14.41%) of the organizations that support research and 12/58 (20.69%) of those that are pursuing drug repurposing. Looking at the 5 organizations that have successfully received FDA approval, only 1 organization (20%) tracks off-label drug use. Of the 12 organizations that use a drug off-label with some measures of success, 5 (41.7%) track off-label drug use. **25/94** (27%) of the drug repurposing projects in the ROADMAP were first identified from off-label drug use data. Among the **17** organizations that track off-label drugs, **5** (29%) of them utilized this data in an ongoing drug repurposing project as a drug identification method.

Though these are all correlational relationships, they do suggest that tracking off-label drug use in your patient population, either informally through simple patient surveys or systematically through a natural history study, can be helpful in identifying potentially helpful drugs for a rare disease.

Also see [\*"Data from off-label use" as an identification method, "off-label use" as an alternative to clinical trials and "off-label use" as an alternative success outcome.\*](#)

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## Providing data/samples to researchers & supporting clinical trials



Rare disease nonprofits have a crucial role to play in the support of research in early stages by facilitating researcher access to existing resources, such as patient registry data, [biobank](#) samples, contact registry information, etc.

In later stages, rare disease nonprofits can support clinical trials in various ways:

- **Clinical trial recruitment:** serving as a resource for researchers and clinical trial PIs to recruit participants while simultaneously actively seeking out and sharing information about clinical trials for their patient population.
- **Patient education:** informing patients of eligible trials and discussing the pros and cons of participation, including potential consequences such as ending up on a placebo, associated costs, or having to stop taking a drug after clinical trial completion.
- **Leading or assisting in clinical trial protocol design:** assisting in the design of clinical trial protocols, depending on their collaboration and expertise. They can act as the administrative PI (writing the protocol, the MOU, and the application to the FDA, even if they do not have scientific or medical expertise) and provide input on protocol design to better represent patient needs and facilitate recruitment. They can also provide expertise on important clinical measures and endpoints.
- **Advocate for certain subpopulations:** adding or coordinating clinical trial sites, facilitating conversations with pharma companies to expand their ongoing clinical trials to include a specific subtype of rare disease patients to a clinical trial, or to add expansion cohorts to ongoing trials.
- **Collaborating with other rare disease nonprofits:** creating opportunities for collaboration such as joint-funding, increasing size of clinical trials, sharing data and samples, etc. For example, basket trials can help defray costs, coordinate efforts, lean on a shared infrastructure and PIs, benefiting multiple rare disease patient populations simultaneously.
- **Funding:** providing either seed funding, which can enable researchers to do preliminary work to then qualify for larger grants for clinical trials, or provide extra funding if external funding is insufficient to support a clinical trial. With enough funding, a rare disease nonprofit can potentially support multiple ongoing clinical trials, i.e. have eggs in multiple baskets to raise the chances of having a successful outcome.

There are many potential benefits to patients if a clinical trial is successful, such as more data on the safety and efficacy of existing treatments for various different patient populations, or new treatment options becoming available for them. There are also other benefits for the nonprofit itself in supporting clinical trials, such as - expanding their patient network, especially internationally. It also provides a great milestone in its mission to support research, which can serve as both internal motivation and help cement the idea that a rare disease

nonprofit is able to be a partner in further rare disease research with pharmaceutical companies and academic institutions.

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## PARTNERING & COLLABORATION SUPPORT



One of the greatest assets of a rare disease nonprofit organization is its ability to weave networks. A network of patients and loved ones becomes a community, where information sharing, support and advice can make a huge difference and combat the fear and anxiety of a rare disease diagnosis. A researcher network can bring together everyone who already is or is interested in doing research related to the rare disease of interest so they can share insights, data, samples and work together to apply for grants and complete work that can save lives. Outside of those two main networks, there are also other opportunities for collaboration that can bring great value to a rare disease community, but may be less known:

- **Collaboration with academics:** making sure the research questions are patient-need-centered, providing funding, access to patient data and samples, helping with clinical trial design, recruitment, education, and forming a Scientific or Medical Advisory board (SAB/MAB). As with any partnership, it's important to initiate a formal contract or clear rules of conduct, in which the nonprofit retains ownership of any data it provides or facilitates the use of, and has access to any research findings that result as a part of the research project it is supporting.
- **Collaboration with pharmaceutical companies and biotech companies:** collaboration with pharma is a roadblock for organizations pursuing drug repurposing 17/58 (29.31%) and one of the main reasons for non-pursuers 31/77 (40.26%). Still, collaborations are possible by aligning interests and incentives. Rare disease nonprofits can initiate these collaborations by inviting pharma representatives to patient and research conferences, and showing them the impact they can have on the patient population; they then can become "internal champions", who can advocate for the interests of the nonprofit internally within the pharma company.
- **Collaboration with other rare disease nonprofits:** connecting with other rare disease nonprofits, whether it is ones that are focusing on the same rare disease, a similar rare disease, or one that doesn't seem to be related at all, can lead to benefits such as combining patient populations, funding, and resources, creating a bigger impact and advancing research for both rare diseases. Overlap such as common drugs, side effects, and comorbidities can lead to new connections between research spaces, potentially resulting in impactful scientific breakthroughs.
- **Collaboration with government organizations:** nonprofits can influence the FDA's policies and guidelines for rare diseases and help to create a more favorable environment for rare disease research. By working with other rare disease nonprofits, they can raise awareness of the unique challenges faced by rare disease patients, such as the lack of treatments and limited access to clinical trials; they can provide feedback on draft guidance documents, participate in public meetings and workshops, and provide expertise on specific rare diseases.

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## PATIENT SUPPORT



Rare disease nonprofits can provide direct patient support in the process of drug repurposing in various ways:

- **Provide treatment-related assistance** to patients by working with insurance companies to ensure coverage and promote patient access to new drugs that have been approved by the FDA, or off-label drugs which have been newly identified or being tested in the drug repurposing process.
- **Facilitate compassionate use access**, which allows patients with a serious or life-threatening disease to access investigational drugs outside of clinical trials, if the patients are not eligible or if the clinical trial does not happen for various reasons.
- **Provide access to a network of physicians** who are the most knowledgeable about the disease and the treatments available, including ones that are involved in drug repurposing projects.
- **Provide access to genetic testing** for patients to determine if they have a specific rare disease and help identify appropriate treatment options, which may lead to the identification of new drug repurposing opportunities.
- **Disseminate rare disease-specific educational information** to patients, families, and healthcare providers through various channels such as their website, social media, newsletters and patient conferences. This may include research results, updated treatment guidelines, lists of ongoing clinical trials, etc.

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## 2. IDENTIFYING THE DRUG

Drug identification is an important early step in the process of drug repurposing. It involves identifying existing drugs that may have the potential to treat a particular rare disease. This can be done through various methods.

We believe these approaches can be separated into five categories:

1. Drug Screen approach (High-throughput Drug Screening)
2. Pathogenesis targeting approach (Preclinical/Translational research)
3. Data from similar diseases approach
4. Computational approach
5. Data from off label use approach



In the ROADMAP survey, **94 (76 unique)** drugs were found to be in process of being repurposed by **40** organizations. The most common drug identification method was preclinical/translational research (**66 drugs**), which can also be referred to as pathogenesis targeting (research identifies a potential problem underlying a disease [e.g., mTOR activation is increased in Castleman disease] and then matches a drug to reverse the problem [e.g., using an mTOR inhibitor to treat Castleman disease], which is then studied further in the laboratory). The other top choices were looking at drugs used in similar diseases (**29**), analysis of off-label drug use (**25**), high throughput drug screening (HTDS) (**21**), and literature review/meta-analysis (**16**). The least common approach involved computational/machine learning/artificial intelligence (**2**), which may speak to the novelty of this approach and its slow integration into the existing research/repurposing processes or that it is mostly being utilized without the involvement of rare disease nonprofit organizations.

### ***Benefits of multiple methods***

These methods of drug identification can be done simultaneously or in sequence, depending on the organization's resources and priorities. For example, an organization may choose to perform a high-throughput drug screen and conduct a literature review to identify a list of candidates and look for overlap between “hits”. Preclinical/translational research can help to identify candidates and help to refine the list to the most promising ones. As each method has certain limitations, using multiple methods can help to increase the chances of success in the drug repurposing process.

In our survey, **57** drugs were identified by more than one identification method. The most common combination of methods was HTDS and Preclinical/Translational research (**11** cases) and looking at drugs used in similar diseases and Preclinical/Translational (**9** cases). This speaks to the value of pursuing multiple avenues at once and triangulating the findings from one method with another. It is also interesting to point out that the **11** drugs were identified as promising by utilizing different identification methods for different rare diseases.



## **ROADBLOCKS & OPPORTUNITIES**

Rare disease nonprofits are often small, volunteer-led organizations. They are susceptible to several internal limitations, which, though applicable to almost all stages of the process, in early stages of the drug repurposing process can become critical roadblocks that can prevent an organization from ever getting to identifying a drug candidate for repurposing:

- **Lack of financial resources:** Not having a sufficient budget limits the ability to conduct necessary research or support certain important resources such as [biobanks](#) or [natural history studies](#). See [“Funding Support”](#) for suggestions on how to overcome this roadblock.
- **Lack of resources:** Without having access to or creating ways to support systematic data collection and data analysis organizations may struggle to identify potential drug candidates or assess their safety and efficacy in clinical trials. See [“Providing data/samples for research”](#) for suggestions on how to overcome this roadblock.
- **Lack of staff:** Organizations that are have little to no full-time staff can have difficulties juggling their primary mission of supporting patients with some time-consuming aspects of early-stage drug repurposing, such as engaging with external collaborations, setting up data and sample collection, and bringing together both the patient and researcher community to identify both the overall research

strategy and promising off-label drugs. See [“Partnering & Collaboration”](#) for suggestions on how to overcome this roadblock.

- **Lack of time / prioritization:** If organizations focus on too many projects at once, this can divert attention and resources away from targeted drug repurposing efforts, limiting the overall impact of these initiatives. See [“Patient-centered research agenda”](#) for suggestions on how to overcome this roadblock.
- **Lack of an existing researcher network:** Without having an established researcher network, it may be challenging to attract researchers to apply for a grant or pursue specific research questions in relation to identifying a drug to repurpose. See [“Research Network”](#) for suggestions on how to overcome this roadblock.
- **Lack of medical expertise among the rare disease nonprofit leaders:** Organizations relying on external advisors to provide guidance on which drug identification is best for their rare disease and budget may face difficulties in securing an advisor that has the level of expertise and commitment to engage with the organization and their mission. See [“Partnering & Collaboration”](#) for suggestions on how to overcome this roadblock.
- **Lack of understanding of the steps towards successful drug repurposing:** Not knowing how best to approach drug repurposing, an organization to be stuck in “limbo”, not knowing how to identify a promising drug or how to proceed once a drug has been identified. It can also lead to mistakes or oversights that may compromise the project's success. The CDCN hopes that [the ROADMAP tool](#) and associated data helps at least partially fulfill this need and help rare disease nonprofits move forward in their drug repurposing journeys.



There is evidence in the ROADMAP data that some organizations have been able to overcome some of these limitations and still be successful. For example, looking at staff limitations: among our 147 organizations, 52 (38.78%) do not have any full-time staff. This includes 34/111 (30.63%) of the organizations that support research and 20/58 (34.48%) of those that are pursuing drug repurposing. Looking at the organizations that have been successful in drug repurposing: 1/5 (20%) of the organizations who have had a drug FDA approved, and 6/12 (50%) of organizations which are using a drug off label with some measure of success do not have any full-time staff. This means that

even if you're a newer or smaller organization, you can bring treatments to patients through repurposing that have an impact on their quality of life in various ways.

Additionally, many RDNPs are able to achieve success outcomes without their leadership team having medical expertise. 79 of the 147 RDNP leaders that participated in the ROADMAP survey (53.7%) noted that they are also either patients themselves or loved ones (often parents) and not researchers or physicians, and 1 (1.27%) of these organizations was able to make it to FDA approval with a repurposed drug, while 4 (5.06%) have been able to get a repurposed drug available off label with some measure of success.

## High Throughput Drug Screening

**High-throughput drug screening** (HTDS) is a method of rapidly screening anywhere from hundreds to thousands of compounds from existing libraries to identify those that have a specific biological activity at the model organism, cellular, pathway, or molecular level. This process is used in early stages of drug discovery to identify potential drug candidates and in drug repurposing to identify new potential uses for existing drugs. Compounds that affect the target in an anticipated way are called hits, and the screens may be restricted to compounds that have already been tested in humans, thereby reducing the need for extensive preclinical tests. These hit compounds become candidates for further repurposing research. A HTDS can produce a huge number of hits, which should then be validated to identify which are most promising to move forward with.

It is important to remember that many hits in high-throughput drug screens do not end up being effective in patients with the given disease. This discrepancy may be due to the cell line or model system not being a good representation of the patient's disease, issues with dosing and timing of administration, or other issues. It is also important to consider that it can be quite expensive, as it requires access to a highly specialized screening facility and compound libraries, which are often offered by Contract Research Organizations (CRO) or core facilities.

Among the **21** drugs identified via high throughput drug screens in our ROADMAP survey, **6** are still in early stages, **6** are in clinical trials, **5** are in late stages, **1** has made it to FDA approval, while **6** are being utilized off label with efficacy/safety data and some subjective measures of benefit, and **3** have been unsuccessful.

Resources:

- [Impact of high-throughput screening in biomedical research - PubMed \(nih.gov\)](#)
- [High-content drug screening for rare diseases - PubMed \(nih.gov\)](#)
- [Drug discovery process powerpoint presentation slides ppt templates \(slideshare.net\)](#)
- [Different Types of Drug Design in BioPharma \(rxcinational.com\)](#)

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## Pathogenesis-targeting approach

**Preclinical/translational research** was the most common drug identification method in our data (**66 drugs**), possibly both to the fact that it's the most traditional research approach and that it likely encompasses a number of different research approaches, including pathogenesis targeting.

**Pathogenesis targeting** refers to the process of identifying and targeting the underlying biological mechanisms or "pathways" that cause a disease. By understanding the pathogenesis of a disease, researchers can identify key molecules or processes that are involved in the disease process, and identify existing therapies that target these specific pathways. For example, the CDCN uncovered that over activation of mTOR was important to the pathogenesis of Castleman disease and then found an approved mTOR inhibitor that it began testing on patients. More about this story [here](#).

**Translational research** describes a process of taking knowledge and discoveries from the laboratory and applying them to patients. There are very many research approaches that can fall into the category of preclinical and

translational research. For example, **proteomics** can be used to quantify all the proteins present in a biological sample, such as a cell, tissue, or organism to understand a disease and identify potential repurposing candidates.

**14** of the drugs identified through preclinical/translational research are still in early stages, **24** are in clinical trials, **9** are in late stages, and **5** have made it to FDA approval. **14** are being used off label with some measure of benefit and **9** have been unsuccessful. It's important to note that **5/5 (100%)** of the drugs that received FDA approval utilized some form of preclinical/translational research in their identification process, **4/5 (80%)** in combination with other methods. The most common combination of drug identification methods in our data was Preclinical/Translational research and HTDS (**11** cases), and Preclinical/Translational and looking at drugs used in similar diseases (**9** cases). This speaks to the value of pursuing multiple avenues at once and triangulating the findings from one method with another. It is also interesting to point out that the **11** drugs were identified as promising by utilizing different identification methods for different rare diseases.

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## Data from similar diseases approach

Rare disease nonprofit organizations can identify promising drugs for repurposing by researching drugs that are used for similar diseases. Genomic analyses (studying the genetic makeup of patients with different rare diseases to identify common genetic mutations or variations that may indicate an overlap), phenotypic analysis (studying the observable characteristics or symptoms of patients with different rare diseases to identify commonalities) and various computational approaches, in which large-scale data sets of genetic, protein, cellular, etc. are analyzed can help to find potential similarities between diseases that may benefit from the same drug.

Looking at drugs used in similar diseases was the second most common choice of drug identification methods for drug repurposing projects (**29 drugs**). This is very interesting as it highlights the potential value of cross-rare disease and cross-organizational collaboration. **2** of these drugs are still in early stages, **9** are in clinical trials, **6** are in late stages, and **3** have made it to FDA approval. **8** are being used off label with some measure of benefit, and **4** have been unsuccessful.

Once a similar rare disease is identified, a rare disease nonprofit organization can pursue a few avenues to learn from their treatment experience to identify potential repurposing opportunities for their rare disease:

**Literature review:** Reading up on all the research on the similar rare disease, to see if any treatments have been proposed but not yet pursued through translational research

**Other rare disease nonprofit organizations:** If the similar disease has an active nonprofit that supports research or tracks off-label drug use, collaborations can be established to share information and resources to identify overlaps which could benefit both populations. Direct organization-organization collaboration may uncover other types of knowledge which is not often published in literature or other official sources, such as their drug repurposing experience and struggles, anecdotal evidence of certain off-label treatments being promising, some unusual disease symptoms or drug side effects which are still unexplained, etc.

**Researchers that focus on similar diseases:** If the similar disease has researchers that are actively pursuing translational work, forming collaborations with them may benefit a rare disease nonprofit's researcher knowledge base and network, by providing a new perspective and insights from similar diseases.

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## Computational Approach

Utilizing AI and machine learning (ML) to identify potential repurposed treatments is a relatively new approach, coming from information and computer science and “big data” computational analysis. It can be done in a variety of ways, which are constantly evolving and improving with the improvement in models, computational abilities. A few of these are:

- **Meta-analysis of literature** using natural language processing (NLP) and other techniques to analyze large amounts of scientific literature and identify potential connections between different diseases, treatments, and drugs. This approach can help to identify new uses for existing drugs and therapies, and can also help to identify new drug targets and mechanisms of action.
- **Mining databases and creating knowledge graphs:** analyzing large amounts of data from various sources, such as electronic health records, clinical trial databases, and drug databases to try to find connections between them. This approach can help to identify new connections between different diseases, treatments, and drugs, and can also help to identify new drug targets and mechanisms of action.
- **In silico screening:** uses structure and ligand-based approaches to virtually screen large collections of compounds computationally.

Each of these approaches can help to accelerate the drug discovery and development process and lead to the identification of new treatments for a wide range of diseases and conditions, though they do require a specialized skill set and access to huge amounts of data.

Using ML/AI approaches was the least utilized type of drug identification methods for drug repurposing projects in our data (**2** drugs). Out of these, **1** drug is in early stages and **1** is in clinical trials; **none** have yet made it to late stages, FDA approval, or are being used off label with some measure of benefit; and none have been unsuccessful.

If you are interested in finding out more about this approach, you can check out **EveryCure** at [www.EveryCure.org](http://www.EveryCure.org), a new nonprofit combining data from a variety of approaches to find all potential treatments for all diseases.

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## Data from off label use approach

Also see [“off-label use” as an alternative to clinical trials](#) and [“off-label use” as an alternative success outcome](#).

**Off-label drug use** refers to the use of a drug for a disease that has not been specifically approved by regulatory authorities, such as the FDA in the US. It is quite common and is used in cases where a drug has been found to be potentially safe and effective for a new disease through research, or a physician has reason to believe it may help a patient from their own medical knowledge or anecdotal reports from other doctors. Additionally, doctors may prescribe drugs off-label for the disease which the drug is approved for, but for a different population, such as children, pregnant women, or other populations, which were not included in the original clinical trials. This can be incredibly helpful for patients that are not responding to the standard of care or have no standard of care for their disease. However, off-label use of drugs can also have risks. Since the safety and effectiveness of a drug for off-label use have often not been established, there is a potential for adverse events or lack of efficacy.

**Evaluating off-label use** of drugs in a rare disease of interest can help to identify drugs that should be studied further for that rare disease.

To be able to utilize off-label drug use as an avenue for drug identification, rare disease nonprofits and researchers can implement one of the following few strategies:

- **Surveys and questionnaires:** Surveys and questionnaires can be used to gather information from patients and caregivers about their experiences with off-label drug use. These surveys can be distributed through the nonprofit's website, social media, or mailing list, and can include questions about the types of drugs being used, the reasons for off-label use, and the outcomes of treatment.
- **[Natural history studies and/or patient registries](#):** Registries can be used to collect and track information about patients with a specific rare disease, including information about the treatments that patients are receiving and its effects (and side effects) over time.
- **Collaboration with healthcare providers:** Nonprofits can collaborate with healthcare providers to gather information about off-label drug use in their patient populations in order to identify trends and patterns in off-label drug use.
- **Literature review:** Nonprofits can help conduct literature reviews of existing studies and publications to identify information about off-label drug use in their patient populations. This can include searching for articles and studies that have been published in peer-reviewed journals, and reviewing data from clinical trials and observational studies. This information can then be provided to the researcher's in the nonprofits' network to evaluate whether any of the drugs are promising enough to pursue.
- **Insurance claims data and/or medical record review:** Nonprofits can look in insurance claims data and medical record data to identify information about off-label use to identify potentially promising drugs for further investigation.

Among the 147 organizations surveyed, only 17 (12%) track off-label drug use within their patient populations. This includes 16/111 (14.41%) of the organizations that support research and 12/58 (20.69%) of those that are pursuing drug repurposing. Looking at the 5 organizations that have successfully received FDA approval, only 1 organization (20%) tracks off-label drug use. Of the 12 organizations that use a drug off-label with some measures of success, 5 (41.7%) track off-label drug use. 25/94 (27%) of the drug repurposing projects in the ROADMAP were first identified from off-label drug use data. Among the 17 organizations that track off-label drugs, 5 (29%) of them utilized this data in an ongoing drug repurposing project as a drug identification method.

Though these are all correlational relationships, it does suggest that tracking off-label drug use in your patient population, either informally through simple patient surveys or systematically through a natural history study, can be helpful in identifying potentially helpful drugs for a rare disease.

Among the 147 organizations surveyed, 17 (11.56%) track off-label drug use of their patient populations. 16/111 (14.41%) of the organizations support research, and 12/58 (20.69%) of those that are pursuing drug repurposing. 2/5 (40%) of the organizations who have had a drug FDA approved reported systematically tracking off-label drug use.

Off-label use of drugs can serve as both a starting point and endpoint for drug repurposing. Rare disease organizations can collect and track data on off-label drugs that patients are already using, and identify the most promising drugs for further research and repurposing. If for some reason FDA approval is not possible for these drugs, they may still be used off-label, but with the added benefit of additional research on proper dosages, potential drug interactions, and side effects.

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### 3. VALIDATING THE DRUG

The validation stage of drug repurposing is a crucial step in determining whether a drug candidate is likely to be safe and effective in treating a specific rare disease and whether it should progress forward to more research. This stage typically involves conducting additional studies, prior to moving forward with giving the drug to patients and/or performing clinical trials. This stage can be separated into in vivo and in vitro studies, as well as preliminary validation through real-world evidence. Once the validation stage is completed, the organization often moves forward with clinical trials to gather more robust data on the drug's safety and efficacy in human subjects with the rare disease. In some cases researchers move straight from identification of a promising repurposing approach directly to treating patients in a clinical trial and/or outside of a clinical trial (off label), bypassing this stage.



### **ROADBLOCKS & OPPORTUNITIES**

The validation stage of drug repurposing drugs for rare diseases faces several challenges in addition to the ones described in the prior stage. These roadblocks are more specific to the requirements of preclinical data and collaboration with external partners, such as academics, researchers, biotech companies, pharmaceutical companies, etc.

- **Limitations of preclinical models:** Preclinical models, or studies conducted in cells, tissues, or animals, before testing in humans, can provide valuable information on the potential effectiveness and safety of a drug. However, preclinical models may not accurately reflect the human version of the rare disease, which can limit the understanding of the drug's potential effectiveness.
- **Limited patient samples:** Rare diseases, by definition, affect a small number of individuals, which can make it difficult to obtain a large enough sample size to conduct meaningful research. Additionally, rare disease patients' samples can also be limited, or access to them may be difficult; they may be spread out geographically, or not available for certain types of research studies. This can make it difficult to conduct research that is representative of the patient population, and can limit the understanding of the drug's potential effectiveness for validation. See [“Providing data/samples for research”](#) for suggestions on how to overcome this roadblock.
- **Lack of real-world evidence (RWE):** RWE refers to data collected in routine clinical practice, outside of the controlled environment of a clinical trial. This type of evidence can provide valuable preliminary information on the safety and effectiveness of a drug in a real-world setting, in a broader patient population and with longer follow-up. In the case of repurposed drugs, there may be limited RWE available, which can make it difficult to gain these insights. See [“Providing data/samples for research”](#) for suggestions on how to overcome this roadblock.
- **Data sharing:** Academic researchers conducting the in vivo/in vitro research for drug validation may be hesitant to share their data, as they may want to be the first to publish their findings. This can slow down the drug repurposing process and make it difficult for the organization to access the information they need. See [“Partnering & Collaboration”](#) for suggestions on how to overcome this roadblock.
- **Differing priorities/timelines:** Academics may prioritize publishing their research findings in scientific journals, which can be important for their career advancement and for the advancement of their field of study. However, this can make it difficult for organizations to access the information they need and delay the timeline of moving forward with the next stages of repurposing. See [“Partnering & Collaboration”](#) for suggestions on how to overcome this roadblock.
- **Intellectual property concerns:** IP refers to the legal rights associated with an invention or discovery, such as patents, trademarks, and copyrights. These rights can be used to protect the creators of the invention and to prevent others from using the invention without permission. In the context of drug repurposing research, IP concerns can arise when academics or organizations have discovered new indications for a repurposed drug, and they want to protect their rights to the intellectual property. This can make it difficult for other academics or organizations to access the information or resources they need to conduct additional research, as they may need to obtain permission or license the IP. See [“Partnering & Collaboration”](#) for suggestions on how to overcome this roadblock.

To overcome these challenges, it is important to supplement preclinical models with other types of research, establish partnerships with other rare disease organizations, various academic institutions and research labs, establish transparent communication channels between stakeholders and clear data ownership and licensing agreements. Open-access platforms and data-sharing agreements can also facilitate greater access to research findings and resources, as well as establishing continuing to fund and support systematic data and samples collection resources.

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## In Vivo Studies

**In vivo studies** are research studies that are conducted in live animals, as opposed to in a laboratory dish (in vitro) or in a computer simulation (in silico). These studies are used to investigate the effects of drugs, chemicals, or other interventions on living organisms in their natural environment. These studies can be an important tool for understanding the safety and efficacy of a repurposed drug for a rare disease. They are used to investigate the pharmacokinetics and pharmacodynamics of drugs, and to test their toxicity, side effects, and efficacy in a living organism.



Small animals such as mice, rats, and zebrafish are commonly used for in vivo research. These animals are relatively inexpensive, easy to handle, and have a short lifespan, which allows for the rapid completion of studies. Additionally, many of these animals have genetic similarities to humans, which makes them suitable models for human diseases. It's also fairly easy to modify these animals to carry a disease-causing mutation and serve as a “model” of the human disease, which helps to inform understanding of the human disease and test drug efficacy to reverse the disease. However, it's important to note that in vivo studies have ethical considerations and are subject to strict regulations. Additionally, results obtained from animal studies may not always be directly translatable to humans, so even drugs which seem promising in animal models may not end up being successful in being repurposed.

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## In Vitro Studies

**In vitro studies** are research studies that are conducted in a laboratory dish or in a test tube, as opposed to in live animals (in vivo) or human subjects (clinical trials). These studies are used to investigate the effects of drugs, chemicals, or other interventions in a controlled environment, using isolated cells or tissues.

In vitro studies are an important tool for understanding the basic mechanisms of disease and the effects of drugs on the activity of enzymes or proteins, or to test the toxicity of chemicals on cells, or the genetic or environmental factors on cells or tissues, and to investigate the underlying mechanisms of disease.

In vitro studies are cost-effective, as they have a lower cost and less ethical considerations than in vivo studies. However, the results obtained from in vitro studies tend to be less reliable than findings from in vivo systems.

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## Evaluation of Real World Evidence

**Real World Evidence (RWE)** refers to data collected in routine clinical practice, outside of the controlled environment of a clinical trial. This type of evidence can provide valuable information on the safety and effectiveness of a drug in a real-world setting, in a broader patient population and with longer follow-up.

In the context of drug repurposing, all RWE data on a potential drug repurposing approach would be “off label”. RWE can come from various sources, such as electronic health records (EHRs), insurance claims data, and patient-reported outcomes (PROs). EHR and insurance claims data contain detailed information on patient demographics, diagnoses, treatments, and outcomes, and can provide a wealth of information on a drug's safety and effectiveness in real-world settings. PROs can provide insights into patients' experiences and outcomes and can be used to gather information on a drug's impact on quality of life.

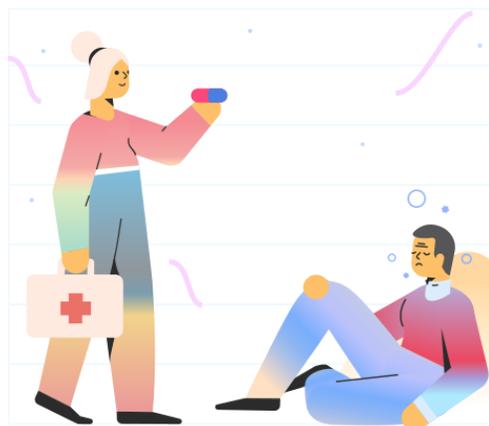
While in vitro and in vivo studies indicating that a drug looks promising for a given disease are notoriously unreliable at predicting whether a drug will work in human patients, clinical RWE data is actual data from that drug in patients and is thus significantly more reliable for validating the potential utility of a drug.

However, in the case of repurposed drugs, there may be limited RWE available, which can make it difficult to determine its effectiveness in the patient population of interest. This can be particularly challenging for rare diseases, as the patient population is small and the disease may have a different manifestation in different patients. Further, confounding variables can make it difficult to assess whether a drug is responsible for the effect of interest outside of clinical trials.

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## 4. UTILIZING THE DRUG CLINICALLY

Once the drug is shown to be promising and potentially safe and effective for a given rare disease, it must be tested in humans to demonstrate whether it is effective or not. This is traditionally done either through clinical trial testing and/or real world off-label use. Clinical trials provide robust data on the drug's safety and efficacy in human subjects with the disease, and are necessary for obtaining FDA approval and making the drug available to patients, while off-label use tracking can provide additional data on the safety and efficacy of the drug in real-world settings.



## ROADBLOCKS & OPPORTUNITIES

Supporting drug repurposing can include a number of challenges related to the clinical trial process itself, which is complex, costly, time-consuming, high-stakes, and requires close coordination of many different stakeholders of varying levels of commitment and interest. Some important roadblocks to keep in mind and be prepared for include:

- **The cost and complexity of clinical trials:** Clinical trials can be expensive and time-consuming. Locating the appropriate clinic and/or physician to conduct the clinical trial may be especially challenging for rare

diseases, particularly those that lack a disease expert who is also a clinical trialist. See [“Funding Support”](#) for suggestions on how to overcome this roadblock.

- **The design of clinical trials:** The design of the trial poses particular challenges with rare diseases, as the selection of appropriate endpoint measures can present challenges due to limited data available or a small patient population. Many rare diseases lack a measurable biomarker, which may make endpoint selection more difficult. When studying a drug in a new disease population, there may be a requirement to redose or reformulate the drug, adding complexity to the clinical trial design and potentially requiring additional safety studies. See [“Supporting clinical trials”](#) for suggestions on how to overcome this roadblock.
- **Lack of a sufficient patient population to study:** There are very few patients who are officially diagnosed with the rare disease, and/or the small patient population may already be receiving the repurposed drug off-label, which can make it difficult to conduct robust clinical trials and gather enough data to support the repurposing of drugs. There might also be limited awareness about the trial, or lack of understanding of the risks and benefits involved. Patients may be hesitant to participate in a trial if they have a distrust of the medical system in general or they fear losing access to the treatment they are currently receiving or go on a treatment during the trial which they might not have access to afterwards. There also may be clinical trials already ongoing, which may further reduce the patient population eligible to enroll in new trials. See [“Patient Network”](#) for suggestions on how to overcome this roadblock.
- **International patient population:** Working with an international patient population can also present challenges in terms of coordinating care and communicating effectively with patients and families with different language needs, different religions and cultural backgrounds. There is also variation in regulations, drug access, research standards and regulatory requirements, and other factors across different countries, which can make it difficult to conduct clinical trials in multiple sites and ensure that all patients have access to the same treatment options during the trial and after its completion.
- **Complexities of rare diseases:** Many rare diseases have several subtypes, symptoms across multiple organ systems, severity of the symptoms, speed of disease progression, or co-occurring conditions which can make it difficult to discern the effects of a repurposed drug in the clinical trial. Due to the rare disease itself, it may be difficult for patients to understand the trial, comply with its requirements, or travel to a trial site; patients who are particularly sick may not enroll in a clinical trial, particularly if the drug is available off-label outside of the trial. See [“Supporting clinical trials”](#) for suggestions on how to overcome this roadblock.
- **Lack of physician support:** Physicians may not be interested in serving as Principal Investigators (PIs) for a rare disease-focused clinical trial, or otherwise support patients during the clinical trial process. See [“Partnering & Collaboration”](#) for suggestions on how to overcome this roadblock.
- **Lack of pharmaceutical company support:** Pharmaceutical companies may not be willing to provide the drug needed to conduct clinical trials, due to lack of financial incentives even if the trial is successful. See [“Supporting clinical trials”](#) for suggestions on how to overcome this roadblock.
- **Blood-brain barrier penetration and other disease-specific considerations:** The blood-brain barrier (BBB) is a specialized system of blood vessels and cells that surrounds the brain and spinal cord that helps protect the brain from harmful substances. This barrier is selectively permeable, which means that some substances can pass through it, while others can't. This means that even if a drug has been repurposed and has been shown to be effective in treating a certain condition, it may not be able to reach the target area in the brain, making it less effective.

- **Regulatory requirements:** Navigating the complex requirements for conducting clinical research can be a huge roadblock for organizations who do not have a core team member who has a research background and/or experience with clinical trials. This is important to consider if the organization is planning to submit the results of the clinical trial to the FDA for approval, as there are certain clinical trial design requirements that need to be implemented. See [“FDA approval”](#) for suggestions on how to overcome this roadblock.
- **Other:** There are other external limitations, such as COVID-related challenges, which caused disruptions to clinical trial recruitment and the ability to conduct in-person study visits.

These limitations can make it difficult for a rare disease nonprofit to support large-scale clinical trials for repurposing. However, by establishing collaborations among rare disease nonprofits, physicians, researchers, and pharmaceutical companies, organizations can work to overcome some of these challenges: pooling resources and expertise, identifying potential trial sites, and creating networks to connect with patients and families affected by rare diseases with ongoing trials for which they are eligible for.

Another strategy is to leverage innovative trial designs, such as basket and umbrella trials, which allow for testing multiple treatments for multiple rare diseases or subtypes in one trial. Furthermore, utilizing digital health technologies, such as telemedicine and remote monitoring, can help overcome geographic and logistical barriers to patient recruitment and retention, while also reducing costs. Regulatory agencies may be more receptive to innovative clinical trial designs for rare diseases, and engaging with them early in the process can help ensure that trial design and data collection are aligned with their requirements. By leveraging patient and community engagement and various types of partnerships, rare disease nonprofits can work to overcome these barriers and advance progress in their rare disease space.

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## Clinical trials

Clinical trials are research studies that are conducted to evaluate the safety, efficacy, and effectiveness of drugs, medical devices, or other interventions in humans, after preclinical work has been done to evaluate potential efficacy and safety. The clinical trial process is divided into several phases, each of which has a specific purpose and set of objectives:



1. **Phase I clinical trials:** These are the first studies in humans. They are usually small, short-term studies that involve a small number of healthy volunteers or patients. The main objectives of Phase I trials are to evaluate the safety and pharmacokinetics (how the body absorbs, distributes, metabolizes and excretes the drug) of the new intervention. This step is typically skipped for repurposed drugs that are already FDA-approved for another disease.
2. **Phase II clinical trials:** These studies involve a larger number of patients and are designed to evaluate the efficacy and safety of the new intervention. The main objectives of Phase II trials are to determine the optimal dosage and to assess the effectiveness of the new drug or device. In many rare diseases, this is

the only clinical trial ever performed and a moderately sized clinical trial indicating that drug works is typically enough to change treatment guidelines and potentially lead regulators to approve the drug for this new use.

3. **Phase III clinical trials:** These studies are large, multicenter studies that involve hundreds or thousands of patients. They are designed to provide more robust data on the safety and efficacy of the new intervention, and to compare it to the current standard of care. The main objectives of Phase III trials are to confirm the effectiveness of the new drug or device and to further evaluate its safety profile. Phase III trials are typically not required for rare disease drug repurposing effort.
4. **Phase IV** studies are done after the FDA approves a drug. These studies are called post-marketing studies, which are done to monitor the safety and effectiveness of the drug in the general population.

Though some drug repurposing projects go through all 3 phases, most are able to skip **Phase I** since basic safety for the drug has already been established in prior research (though if the patient population is very different from the original, Phase I trials may be warranted). In some cases, only a single clinical trial (often considered “phase II”) is needed to evaluate the effectiveness and safety of a repurposed drug to change treatment guidelines and potentially lead regulators to approve the drug for this new use.

After clinical trial completion, some researchers/organizations may proceed with submitting the data to the FDA to decide whether to approve the drug or device for use in the new disease. However, other researchers/organizations do not submit data to the FDA and choose to publish the study in a medical journal article and use the data to support recommendations to use the drug “off-label”. This decision is based on the fact that the time and cost of clinical trials are significant, and the process of submitting the application to FDA is very difficult without the support of the pharmaceutical company who owns the drug patent. Even with support, it takes years for companies to put together the documentation packet, which is often several hundred pages long.

As discussed in other sections, there is much complexity in the design, funding, recruitment and management of clinical trials. Here we would like to point out a few clinical trial designs which might be especially useful for repurposing work in rare diseases, as they are able to potentially save time and money, and benefit multiple patient populations simultaneously:

- **Basket trials** are a type of clinical trial that are used to test the effectiveness of a drug in treating multiple different diseases or subtypes of a disease, who all have a specific genetic mutation or biomarker in common.
- **Umbrella trials** are a type of trial that test a drug in a group of patients with different diseases or subtypes of a disease based on a common theme such as a similar pathology or biology.
- **N-of-1 trials**, also known as "single patient trials" are a type of clinical trial that are used to test the effectiveness of a drug in a single patient, rather than in a group of patients. These trials can provide personalized treatment options for that person, as well as provide vital insights into the disease and treatment effectiveness, and provide justification for conducting larger trial. This is an especially important option for ultra-rare diseases in which large-scale clinical trials are simply impossible or for rare disease organizations which cannot financially support clinical trials.

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## Off-label use

Also see [“Data from off-label use” as an identification method](#) and [“off-label use” as an alternative success outcome](#).



**Off-label drug use** refers to the use of a drug for a disease that has not been specifically approved by regulatory authorities, such as the FDA in the US. It is quite common and is used in cases where a drug has been found to be safe and effective for a new disease through research, or a physician has reason to believe it may help a patient from their own medical knowledge or anecdotal reports from other doctors. Additionally, doctors may prescribe drugs off-label for the disease which the drug is approved for, but for a different population, such as children, pregnant women, or other populations, which were not included in the original clinical trials. This can be incredibly helpful for patients that are not responding to the standard of care or have no standard of care for

their disease. However, off-label use of drugs can also have risks. Since the safety and effectiveness of a drug for an off-label use have not been established, there is a potential for adverse events or lack of efficacy.

In the context of clinical use during a drug repurposing project, off label use refers to giving the drug which may be promising to rare disease patients and then systematically capturing data to evaluate if it's helpful, and if it is, considering moving forward clinical trials.

Off-label use is not only a precursor, but also an alternative to clinical trials if the latter are not feasible due to costs, patient size, lack of researcher or pharma support, etc. This is why it's so important for a rare disease nonprofit to have infrastructure, whether informal such as a patient survey or a [formalized natural history study](#), to be able to **capture and track off-label drug use**. This will enable the nonprofit to not only be able to have a list of all drugs being prescribed or taken OTC for their rare disease of focus, but also track their effectiveness and side effects over time. This can be vital data to provide to researchers, and can be a stepping stone to more formal research, such as clinical trials, in the future.

Off-label use often occurs before, in parallel to, and/or after a clinical trial is performed to rigorously evaluate whether a drug is effective or not. And sometimes a clinical trial is never performed and the drug is used off-label for many years.

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## 5. REACHING AN OUTCOME



There are many ways we can conceptualize “success” in a drug repurposing project. One obvious and traditional marker is receiving FDA approval, but it is important to note that there are many factors that affect whether a drug can ever get FDA approval that do not depend on its safety, efficacy and are beyond the control of a researcher or a rare disease nonprofit organization supporting a drug repurposing project.

Notably the most important of these is that pharmaceutical companies may choose to not invest time and money into supporting the FDA approval application. Thus, we consider FDA approval as one metric among others. The ultimate goal is to ensure that drugs that can be effective and safe for a rare disease are used for that rare disease, regardless of if it's following an FDA approval, treatment guidelines changes, or off label use with some efficacy/safety data and measures of benefit.

Some of these outcomes are final endpoints for a repurposing project, such as FDA-approval, while the others - off-label use and abandonment - can be reached at earlier stages in the process. A project can be abandoned at any stage, whereas off-label use can be considered a sufficient success endpoint whenever there is sufficient evidence on a drug's safety and efficacy data, and it's integrated into treatment guidelines. In some cases, this can be achieved without formal clinical trials.



## **ROADBLOCKS & OPPORTUNITIES**

Even if a drug shows promising results in preclinical and/or clinical studies, it may still face roadblocks in the final outcome stages.

### **FDA approval process requirements**

The FDA approval process for repurposed drugs can be challenging and time-consuming. The FDA may require additional clinical trials and data to establish the safety and efficacy of repurposed drugs for new indications, the overall document which needs to be submitted can be hundreds of pages and can take months of work to put together. Without the support of a pharmaceutical company, the avenue for FDA approval is limited to a "citizen's petition", which does not have a good track record of being successful often. There is little/no FDA guidance for how rare disease nonprofits can best spearhead drug repurposing initiatives and many have had difficulty navigating the regulatory requirements for repurposed drugs. Repurposed drugs for rare diseases may qualify for orphan drug designation, FDA breakthrough designation, and other similar programs, which could provide financial incentives and expedited review. However, the criteria for qualifying for these statuses can be restrictive, and not all repurposed drugs may qualify.

Additionally, even if the drug is FDA-approved or if available off-label with with some efficacy/safety data and measures of benefit, there are still some important roadblocks to consider:

- **Drugs may not work for everyone:** Even if drugs are successfully repurposed, they may not work for all patients, even if they have the same rare disease or even the same rare disease subtype. This can be due to a variety of factors, such as genetic variations, differences in the underlying causes of the disease, or other individual patient characteristics. See ["Patient Support"](#) for suggestions on how to overcome this roadblock.
- **Side-effects:** As with any treatment, repurposed drugs may have side effects, which can vary in severity. Some side effects may be minor and manageable, while others may be more severe and have a significant impact on the patient's quality of life. This can be particularly challenging for rare disease patients, as there may be limited treatment options available and the side effects of the repurposed drug

may outweigh the benefits for some patients. See [“Off label use”](#) for suggestions on how to overcome this roadblock.

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- **Limited supply:** The supply of repurposed drugs can be a challenge as they were originally approved and manufactured for a specific indication. If the demand for the drug increases for a new indication or several new indications, it can be difficult to obtain enough supply if the manufacturing does not increase to meet this new demand. Moreover, if the drug is repurposed for more common diseases, such as COVID-19, it could affect the supply for rare disease patients.
- **Physician prescription:** Physicians may not be aware of off-label uses of drugs for rare diseases if they do not see many patients with those conditions. Therefore, it is crucial for rare disease organizations to educate not only physicians in their network, but also the patient and loved one community about potential off-label treatment options, so that they can advocate for themselves and make informed decisions about their care. See [“Patient Support”](#) for suggestions on how to overcome this roadblock.
- **The cost of drugs:** whether off-label or FDA-approved, drugs can present affordability challenges for patients, particularly if they are not covered by insurance, or are covered by some insurance in some cases, while not in others. See [“Patient Support”](#) for suggestions on how to overcome this roadblock.

To work on overcoming these challenges, various strategies can be employed, such as the development of precision medicine approaches and additional biomarkers to identify patient subgroups that are more likely to benefit from the drug, as well as rigorous monitoring of patients for side effects, collaboration between drug manufacturers and rare disease nonprofits to increase drug supply, and education of physicians and patients on off-label uses of drugs for their rare diseases. Additionally, rare disease nonprofits can lobby for healthcare systems to improve insurance coverage for repurposed drugs and provide financial support to rare disease patients.

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## FDA-Approval

The **Food and Drug Administration (FDA)** is a federal agency within the United States Department of Health and Human Services that is responsible for ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices. The FDA is also responsible for ensuring that these products are accurately labeled and that they meet the standards set by the federal government.



The process of getting a drug approved by the FDA is a multi-step process that can take several years to complete. The FDA reviews the data from preclinical and clinical studies, as well as other information about the drug, such as its chemical composition and how it is manufactured. If the FDA determines that the drug is safe and effective, it can approve the drug for marketing in the United States. The FDA also plays a role in monitoring the safety of drugs once they are on the market. The agency can issue safety warnings, require post-marketing studies, or even withdraw a drug from the market if it is found to be unsafe.

For **drug repurposing**, the FDA may review and approve the new use of the drug. This process typically involves a new drug application (NDA) or a supplemental NDA (sNDA) which must be submitted by the sponsor (usually a pharmaceutical company) before a clinical trial is performed. The FDA will review the data from preclinical and clinical studies, as well as other information about the drug, such as its chemical composition and how it is manufactured.

The FDA has special provisions in place to expedite the development and approval of drugs for rare diseases, also known as orphan diseases, which are defined as diseases that affect fewer than 200,000 people in the United States. These provisions are intended to encourage the development of treatments for these diseases, which may not be as profitable as treatments for more common diseases.

1. **Orphan Drug Designation:** The Orphan Drug Designation program provides incentives for companies to develop drugs for rare diseases. These incentives include tax credits for clinical trial expenses, a waiver of the FDA application fee, and an exclusive marketing period for the drug once it is approved. [Source](#)
2. **Accelerated Approval:** The FDA can grant accelerated approval to drugs for rare diseases based on a surrogate endpoint, which is a marker that is believed to predict clinical benefit, but has not been confirmed by clinical trials. [Source](#)
3. **Expanded Access:** The FDA also has a program in place to provide access to experimental drugs to patients with rare diseases who have no other treatment options. This program is known as expanded access, or "compassionate use." [Source](#).
4. **Priority Review:** The FDA can also grant priority review to new drug applications for rare diseases. This means that the FDA will expedite the review process for these applications and aim to take action within 6 months (instead of 10 months) of receipt. [Source](#)
5. **Citizen's petition:** A citizen's petition is a formal request submitted to the FDA by an individual or organization, asking the agency to take a specific action related to the regulation of a drug or device. Citizen's petitions can be submitted by anyone to request a wide range of actions from the FDA, such as requesting that the FDA approve a new drug, withdraw an existing drug from the market, change the labeling of a drug, or take action on drug repurposing. [Source](#)

It's important to note that the FDA's approval process for drugs for rare diseases can be complex, and the agency may require additional data and information before approving a drug. Also, historically drug repurposing projects that do not have support of the pharmaceutical company that owns the drug patent or was the original patent holder have not been successful in being able to support FDA approval submissions due to the costs and documentation requirements necessary. Additionally, FDA's role is to ensure the safety and efficacy of the drugs, which means that even if a drug is approved for a rare disease, it may not be covered by insurance or accessible to all patients.

In our ROADMAP survey data, only **5 drugs** (out of our 94 total or 76 unique) drugs, have made it to FDA approval:

1. **Dupilumab** // Eosinophilic diseases
2. **Selumetinib** // Neurofibromatosis
3. **Alpelisib** // CLOVES syndrome
4. **Rituximab** / Pemphigus, Pemphigoid
5. **Sirolimus** // Lymphangioliomyomatosis

Looking closer at the 5 organizations which have had a repurposed drug make it to FDA approval, they are on average **25.8** years old (range: **11 - 44**); their annual funding ranged from **\$100,000** to **more than \$5,000,000** (the most common selection was “**\$1,000,000 and \$2,000,000**”); and they have the following characteristics: **all 5** have an SAB/MAB, **3** have a natural history study, **3** have a formal research agenda, **3** already have an FDA approved drug prior to pursuing drug repurposing, **2** have a patient registry, and **1** has a [biobank](#). One of these organizations has no full-time staff, relying entirely on volunteer or part-time staff to achieve their success, while the other four have anywhere from **1** to **40** full-time staff.

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## Off-label use

Also see [“Data from off-label use” as an identification method](#) and [“off-label use” as an alternative to clinical trials](#).

Off-label use of a repurposed drug that has been shown to be safe and effective through either preclinical and/or clinical research can provide access to treatments for patients, bypassing the regulatory hurdles, costs, and delays associated with FDA approval submissions. Additionally, the clinical trial protocol for such a drug may be streamlined as it is not intended for FDA submission, which could save resources for both the researcher and rare disease organization.

Thus, as an alternative to FDA approval, we can consider a drug to have reached a success outcome when it is available off-label, with efficacy/safety data and some subjective measure of benefit, such as:

- Drug to provide a significant reduction in symptoms
- Significant improvement in quality of life
- Increase life expectancy / decrease in mortality
- Provide cure of disease
- Provide prevention of relapse

Though it is worth considering that due to the fact that it is difficult to qualify what a “significant” reduction or improvement is, these measures are open to various biases and inaccuracies from both reports from patients as well as perceptions of benefit overall from rare disease organizations.

If we look at organizations that fit this criteria from the ROADMAP data for at least one repurposed drug, we end up with **12** organizations. They are on average **17.6** years old (range: **2-44**); the majority (**4 organizations, 33.33%**) reported annual funding between **\$100,000 and \$500,000**; and they have the following characteristics: **11 (91.67%)** have an SAB, **6 (50%)** have a [natural history study](#), **7 (58.33%)** have a formal research agenda, **6 (50%)** have a patient registry, **5 (41.67%)** have a [biobank](#), and **3 (25%)** already have an FDA-approved drug prior to pursuing drug repurposing (one organization has two FDA-approved drugs). Interestingly, **6 (50%)** have no full-time staff, relying entirely on volunteer and/or part-time labor to achieve their success.

Among these **12** organizations, there are **44** unique drugs being repurposed. The most common drugs among these organizations were **Sirolimus (3 organizations)**, **Trametinib, Everolimus, and Bevacizumab (2 organizations)**

each). The most common identification method for these drugs was **Preclinical/Translational research (30)**, closely followed by **data from similar diseases (17)** and **off-label use (17)**. Most of these drugs are currently in early stages or clinical trials, specifically in **recruiting patients for clinical trials (18)**. Their respective rare diseases have the following characteristics: **11 (91.67%)** have animal models, **8 (66.67%)** have cell lines developed, **9 (75%)** have an identified genetic mutation, **8 (66.67%)** have an ICD code, **7 (58.33%)** have treatment guidelines, **5 (41.67%)** have a clear understanding of etiology or disease pathogenesis, and **3 (25%)** have predictive biomarkers.

It's important to note that off-label use of drugs can serve as both a starting point for repurposing as a way of identifying a promising drug, a way of validating a drug through analyzing RWE of its during the repurposing process, and as a success endpoint for drug repurposing. It is also vital to continue monitoring the use of these drugs through natural history studies or patient surveys, to track any potential side effects or other issues that may arise.

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## Abandoned

Though this outcome is listed at the end of the ROADMAP, a drug repurposing project may be abandoned at any stage of the process. Some of the common reasons include:

- **Lack of efficacy:** If preclinical or clinical studies do not show that the drug is effective in treating the new indication
- **Safety concerns:** If the drug is found to have significant side effects or safety concerns
- **Lack of funding:** Drug repurposing projects can be expensive, and if funding is not available to continue the project at any point
- **Lack of interest from pharmaceutical companies:** Pharmaceutical companies are often the sponsors of drug repurposing projects, and a company may not be interested in pursuing a particular project, either at all or past a certain point
- **Difficulty in recruiting patients:** It may be difficult to recruit enough patients for clinical trials
- **Regulatory hurdles:** The process of getting a drug approved for a new indication can be complex and time-consuming, and the project may encounter significant regulatory hurdles
- **Competitive landscape:** There may be already other drugs available that are more effective in treating the same indication
- **Lack of commercial viability:** If the repurposed drug is not seen as commercially viable, it may not be attractive to the pharmaceutical companies to support repurposing.



And though “abandoned” as a status has a negative connotation, it is very important to be able to filter out which drugs are most promising and which are not, and overall, having some drugs be abandoned can speed up the process of getting one that can bring the most value to the patient population.

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