Future Directions for Undiagnosed Diseases Research: the UDN and Beyond

March 21, 2016

Workshop Report

Recommendations Summary

On March 21st, 2016 a group of stakeholders was convened to review thoughts on the Undiagnosed Diseases Network (UDN) and recommendations on possible continuation including: needs, gaps, and opportunities. Participants proposed the following recommendations for consideration in each of six question areas that were discussed. The original questions for each area are also included below in italics.

Intensive Clinical Evaluation

What benefits and components of the UDN clinical evaluation are most important clinically and scientifically? How can the clinical evaluation be optimized to ensure consultants have time to deliberate and improve diagnostic evaluations for the benefit of the patients? Should clinical sites have focus areas of clinical expertise?

- Genotype versus phenotype first, what is the best practice?
    - Need to make sure both sets of data (genotype and phenotype) are captured regardless of which is done first.
    - Best practices will likely depend on the clinical, financial, and geographical needs of the patient.
- Consider collection of environmental, history, and epigenetics data to consider potential interactions, but be wary of small sample size.
- Consider a reasonable minimum core dataset across the network, some standard phenotyping and uniformity to allow for recognizing patterns in the data.
- Patients should have a local workup prior to their visit to a UDN Clinical Site. However, UDN Clinical Sites with focused expertise were seen as having both pros and cons.

Transitions of Care

When is a UDN evaluation "complete"? What is the appropriate management of cases where a diagnosis is not made? How long are patients followed? What patient-centered outcomes should be documented?

- Primary mission of the UDN should be diagnosis, but the group will need to consider its impact beyond diagnosis, and how the process changes the life of a patient and family.
    - Need to transition patients back to the clinical care setting.
    - Research utilization to help diagnose patients is also still important, existing resources and collaborative networks should be leveraged.

- The UDN will need to develop a standard plan for what happens after the UDN evaluation is complete (e.g., re-contacting patients, collaborating with outside clinicians for long term care).
- UDN patient diversity should be captured, evaluated, and refined to inform future versions of the UDN.

Patient and Family Partnership

What are the priorities going forward? What can the UDN uniquely do? How much should patients and families be engaged in the UDN (self-phenotyping, patient pages, outreach, and return of results)?

- Consider studies of patients and families psychological perspectives.
    - Is there a way to classify and better support patients and their families based on their preferences? It may be helpful to engage with families sooner in the clinical evaluation.
- The UDN needs to set clear expectations of what care and services participants will receive as part of the study.
- Create a patient advisory group.
- Partner with the National Organization for Rare Disorders (NORD) and other support groups to develop a patient mentorship model.
- Advertise the services that the UDN provides.

Training, Sharing, and Collaboration

How can the UDN continue to connect the data generated to existing resources and databases? What role and level of support should collaborations have? Collaborations include: collaborative clinical sites, gene function studies, and scientific research collaborations with the UDN. Should the UDN become more international? Should the UDP training component be continued, changed, or expanded to the UDN as a whole to disseminate the UDN model?

- More training is needed to expand expertise.
    - Expand training outside the UDN; develop a “blueprint” for other programs.
    - Develop a curriculum.
- Increase UDN collaborations.
    - Bring in health care providers.
    - Establish international collaborations for case matching, data sharing and identification of ethnic-specific variants.
    - Start patient collaborations with groups for mentorship and support.
- Explore opportunities to connect data.
- Increase funding for functional studies, consider new methods for funding small awards (such as public/private partnerships), and ways to match researchers with the data generated by the UDN.

The Virtuous Cycle and Integrating Data

How can the UDN continue to foster synergistic interactions among clinical and research communities? What are the best strategies to optimize recruiting basic scientists with appropriate expertise to the study of candidate clinical cases? How can integrating data help the UDN model become a community standard of clinical care?

- Emphasis should be placed on diagnosis including mechanistic studies that can be used to help make a diagnosis.
- Need more funding for mechanistic studies if the emphasis on mechanistic studies for diagnosis or follow-up research is increased.
- The UDN model should have synergies and interactions within and amongst sites.
- Finding the right researcher for follow-up studies is key.

Moving the UDN Forward

What are the end goals for the UDN? What can the UDN uniquely do? What is the vision/mission? What is the best strategy to optimize the outcomes from the UDN in both clinical evaluation and discovery (diagnoses and research)? How will the UDN be sustained without CF support and how do we get there? What is the advantage of being a network?

- The UDN should continue and the NIH will need to think about how to fund the UDN during and after a second phase for long term sustainability.
- The focus of the UDN should remain on the diagnosis of patients.
- Develop practices for patient follow-up after a diagnosis.
- Develop ways for other clinical groups to access UDN resources and collaborate with the UDN.

Video of the Workshop and Background Documents

Available at: http://www.genome.gov/27564304

Minutes from the Workshop

Welcome, Context, and History of Program (*Eric Green and Walter Koroshetz*)
Dr. Green provided history on the genesis of the NIH Undiagnosed Disease Program (UDP) and its evolution into the current Common Fund supported UDN. Dr. Koroshetz provided context on the Common Fund and why this workshop was important to the phase II continuation process for the UDN.

Lessons from the UDN (*William Gahl*)
Dr. Gahl described lessons learned from the UDP and how they influenced the creation of the UDN network-wide protocol and current UDN operations.

- Consent forms were written broadly and patients can be re-contacted.
- Currently the UDN is in the process of forming a patient engagement group. This user group could meet a few times per year.
- The Coordinating Center (CC) has been looking into collaborative case solving to educate a larger audience (Grand Rounds) as well as ways to crowdsource unsolved cases with a focus towards clinicians.

Results of RFI and Goals of Workshop (*Anastasia Wise*)
Dr. Wise gave a brief overview of the UDN and more information on the Common Fund phase II continuation process. Results of the Request for Information (NOT-RM-16-001) were also discussed and their influence on the six questions selected for discussion during the workshop.

- Currently the UDN is on target with applications and number of acceptances to meet the year 1 goals of 150 patients seen at the NIH UDP and 25 at each of the other UDN clinical sites.
- Helpful to sequence trios in order to reach a diagnosis.
- Economic barriers for UDN application (costs for tertiary check-ups which are necessary for qualification) preclude inclusion of some underrepresented populations.

Experience of a Recent UDN Patient (*Brendan Lee*)
Dr. Lee presented the evaluation of a recent UDN patient seen at the Baylor College of Medicine Clinical Site. Details of the evaluation process and how important interactions are amongst members of the network were described.

Workshop Questions

Q1 - Intensive Clinical Evaluation (*Framer: Laura Mamounas. Perspectives: Calum Macrae and Cynthia Powell. Moderator: Jonathan Mink.*)
What benefits and components of the UDN clinical evaluation are most important clinically and scientifically? How can the clinical evaluation be optimized to ensure consultants have time to deliberate and improve diagnostic evaluations for the benefit of the patients? Should clinical sites have focus areas of clinical expertise?

- Clinical exome sequencing is becoming more common and the UDN will have to contend with patients bringing externally generated data. Patient exome data are often reanalyzed, sometimes resulting in diagnosis.
- Comfort level of physicians to make a diagnosis using sequence data is a challenge that needs to be addressed for broad implementation.
- The UDN may want to think about distinguishing between undiagnosed and unknown/undescribed diseases
- The UDN is still determining whether it is better to phenotype or sequence first. Best practices may vary from case to case. Furthermore, the UDN's deep phenotyping may be unfeasible for general implementation.
- Are environmental exposure questionnaires included in the standard workup? Older relatives, such as grandparents are valuable sources for information about childhood exposures. Environmental history is now a standard part of the UDN clinical process. Some data can be collected via mail or electronic means, but physiological measures would need to be done at specific centers.
- The UDP has seen cases where the correct diagnosis could be made from the information in the medical records, but was not made. It is difficult for a single physician to be familiar with all of the numerous clinical and research aspects of these complex cases. ~90% of prior UDP cases had some genetic basis. Even though the majority of these cases are congenital, genotyping does not necessarily need to precede phenotyping. Half the diagnosed cases in the UDP have been solved using NGS, and the other half using more traditional molecular techniques (enzyme assays, etc.).
- The UDN should include underrepresented patients. How do we achieve patient diversity? Applicant and patient demographics could be recorded in the UDN.
- Applicants coming from rural areas are not as likely to have access to a tertiary care workup which is needed for consideration for admission to the network. Consultations with referring physicians and metrics to record referrals of UDN applicants to other clinical care should also be counted as impacts of the UDN.
- The UDN should quantify the diagnostic yield of deep phenotyping versus sequencing first. Generating deep phenotype data and linking it to genetic data is a valuable process in and of itself though. That value is lost if not performed.
- Some attendees believed that clinical application of epigenetics could also be explored. Others disagreed and felt that rigorous exploration would require a much higher budget and UDN resources would be better allocated elsewhere.

Summary:

- Will need further discussion on the idea of phenotyping first vs genotyping first. There is likely no one right answer and it is most important to make sure both types of data are captured.
- Develop ways to look at environmental interactions.
- The UDN should also discuss the need for a minimum core dataset across the network.

Q2 - Transitions of Care (*Framer: Jyoti Dayal. Perspectives: Christine Eng and Susan Berry. Moderator: Darcy Kreuger.*)

When is a UDN evaluation “complete”? What is the appropriate management of cases where a diagnosis is not made? How long are patients followed? What patient-centered outcomes should be documented?

- How will UDN clinicians transition care back to referring physicians?
    - Some patients require more resources than others.
    - Sometimes patients will not want to go elsewhere, and UDN clinicians may be the referring physician.
    - It will be important to partner with patients in order to more easily direct them to the next phase of their care (i.e. long-term management with intermittent UDN involvement).
    - Following patients prospectively for patient centered outcomes and healthcare utilization could help prove the value of the UDN as a diagnostic service and inform sustainability plans.
- Is genetic counseling incorporated as part of the visit to a UDN Clinical Site? Is there any effort to identify sites that have expertise in dealing with that disease?
    - Genetic counselors are an integral part at the UCLA Clinical Site and in the UDN in acting as a liaison for the patient. Sometimes, the diseases are so new or rare that there are no experts.
- Are there efforts to bring other patients into the UDN from abroad that match patients seen in the UDN for follow-up research?
    - The UDN has not focused on a matching process, but rather undiagnosed cases.
- Should there be sub-specialty focused UDN sites?
    - There are benefits and hindrances that are associated with binning patients like this. It creates efficiencies in patient evaluation, however, many diseases involve multiple systems and it would be difficult to classify a patients potentially limiting access.
- Sites are doing things differently and it will be important to capture the variability in patient care across the network.
- Is there some way to leverage CTSAs for follow up?
- Is there a way to make a codified network of experts for referral?
- Potential for telemedicine to cover geographically isolated areas.
- Patient follow up:
    - The UDN does a follow up questionnaire after the Clinical Site visit and each year after. There is a need to find a transition for the research aspect as well. An encyclopedia of experts resource would be useful.
- The UDN is also instituting a Grand Rounds Series. Can be used as a forum to reach out to other undiagnosed diseases programs and has the potential to become an outreach effort.

Summary:

- Primary mission is diagnosis.
- Also impact beyond mission in how the UDN change the lives of patients. How are resources utilized? How can the UDN model be translated into the clinical setting? Some translation to clinical settings may impact patients access to research aspects of

the UDN. Research utilization to help diagnose patients is also still important, existing resources and collaborative networks should be leveraged.
- Need a standardized plan for what happens after the diagnosis.
- Capture diversity within the network.
- Network longevity - future versions of the network beyond what currently exists may leverage existing resources in order to follow patients long term and will likely need to develop resources to continue to do so.

Q3 - Patient and Family Partnership (*Framer: John Mulvihill. Perspectives: Vandana Shashi and Donna Appell. Moderator: Judith Hall.*)
What are the priorities going forward? What can the UDN uniquely do? How much should patients and families be engaged in the UDN (self-phenotyping, patient pages, outreach, and return of results)?

- Things to think about when talking about family needs: family mentorship programs and support groups, psychological dimensions of patient care,
    - The UDN will want to consider partnering with support groups and educating both patients and physicians.
- What do we want to learn from and give back to the families who participate?
- Standardized tools are currently being used to assess well-being. Genetic Counseling Outcomes Scale measures feelings of empowerment as a result of participating in the UDN over time. Adding more measures may be more of a burden on patients as they are bombarded with surveys and tests during the one week clinical evaluation. Clinicians feel that resources should be devoted to the primary mission of diagnosis as opposed to increasing assessments of psychological well-being.
- May want to develop overarching questions regarding patient care (e.g. a patient's family social dynamics). Would it be prudent to assign a specific question to each site?
    - Comparisons of patient-provided phenotyping to physician generated phenotyping could be valuable.
- Help families with the "what next?" problem.
    - It may be useful to establish the idea of a process associated with diagnosis, death and dying, psychological support that patients and families need, helping families with "what's next?" Important to empower local physician and patient partners. Bringing families together after diagnosis?
- Patients may want different levels of information even if it does not change the treatment.
- When patients are diagnosed with rare diseases, they often come to NORD, where they are often referred to patient organizations. Sometimes, there aren't institutions that can support their needs for very rare conditions or newly diagnosed patients.

Summary:
- Analyze how patients go home, e.g. patient follow up after their clinical center visit. Different approaches in different parts of the network may be beneficial.
- Create an advisory group that provides feedback to the UDN.
- Partner with NORD and other support groups to develop a patient mentorship model.

Q4 - Training, Sharing, and Collaboration (*Framer: Carson Loomis. Perspectives: Rachel Ramoni and Ronald Cohn. Moderator: Marishka Brown.*)

How can the UDN continue to connect the data generated to existing resources and databases? What role and level of support should collaborations have? Collaborations include: collaborative clinical sites, gene function studies, and scientific research collaborations with the UDN. Should the UDN become more international? Should the UDP training component be continued, changed, or expanded to the UDN as a whole to disseminate the UDN model?

- To better disseminate the UDN model, attendees proposed cataloguing and evaluating the existing training across the UDN to identify current training gaps.
- Training focuses on technical aspects of UDP (e.g. bioinformatics) and many aspects of training are not covered. Gaps include training for patient follow-up.
- From the diagnoses that are made, are you evaluating the system to make it more efficient? This information should be distributed throughout the community.
- Is there a need for a new genetic specialty for analysis of data obtained from the lab? Training should exist at tertiary care centers for someone to do this kind of work. Clinicians are likely not the people that should be doing this kind of work. Variant curation is a specialized field, and there will likely be a certificate program at Baylor College of Medicine soon. This program would be analogous to medical biochemical genetics program, and could likely be a pathway for PhDs. The UDN should develop a strategy to make sure that those in training know what to do to evaluate the patient data. There is potential to implement a defined curriculum at established clinical centers.
- Lots of time is spent trying to accomplish a transition of the patient from the clinical research center to an expert in the field.
- All sites could contribute to a core curriculum to implement nationwide. Need to include training organizations to build the infrastructure needed for such a curriculum.
- How does the relationship with Centers for Mendelian Genomics work? Are data shared directly?
    - Centers for Mendelian Genomics data are fed into Matchmaker Exchange through a different node.
- International and domestic collaborations - looking beyond the UDN to sustainability: Discussions with international programs (Italy, Japan, Australia, etc.) have been largely beneficial, in that discussions with peers provide insight into shared challenges.
- Has the network thought about bringing healthcare providers on board? They might help the network better understand their practices and policies.
    - It can be hard for clinicians to work with payers in terms of the diagnostic odyssey. Payers are less concerned about clinical utility, as it is a vague term with a many definitions and are instead more swayed by the economic impact. Many of the challenges for the payers are state driven. Payers demand empirical data from study designs. The financial burden of the diagnostic odyssey is not as recognized in the US, as patients are only with one payer for 18 months on average. Clinical utility discussion needs to be reframed.
    - The diagnostic odyssey may not be a tangible outcome in the near future. Value based health systems will need data about health outcomes, which will necessitate the development of an accepted definition. Such a definition may not

be universal. There is potential in bringing on healthcare providers into the next phase of the UDN.
    - Attendees emphasized the value of drilling down to a molecular level of diagnosis, however, this may not always be necessary and other patient outcomes matter.

Summary:

- More training needed and should be expanded outside of the UDN.
- There is potential for development of a new curriculum for training.

Q5 - The Virtuous Cycle and Integrating Data (*Framer: Donna Krasnewich. Perspectives: David Koeller and Stephen Prescott. Moderator: Jonathan Mink.*)

How can the UDN continue to foster synergistic interactions among clinical and research communities? What are the best strategies to optimize recruiting basic scientists with appropriate expertise to the study of candidate clinical cases? How can integrating data help the UDN model become a community standard of clinical care?

- Setting any goals of establishing a standard of care will be difficult, don't have resources or knowledge to implement now in the broader community.
- When patients are misdiagnosed extraneous tests are ordered or drugs are inappropriately prescribed.
- UDN clinicians should focus on actionable items once a diagnosis is made.
- Funding is needed to support the development of bioinformatics tools to better integrate data.
- How should medical and graduate curricula for geneticists be structured to better incorporate translational aspects?
    - Researchers/PIs could invite MD/PhDs to their labs.
    - Clinicians and researchers use different lexicon. Building language so that everyone can talk together is a big step.
    - The UDN could sponsor a conference like the experimental therapeutics summer conference in Aspen, to train young people interested in the field.
    - Encourage scientists to participate in Matchmaker Exchange, but basic scientists are not familiar with.
    - Bringing patient cases to basic scientists makes the case more real and changes attitudes of basic scientists who do research on a particular case.
    - When UDP started it had few cases went all the way from diagnosis to treatment, but takes a long time and not scalable.
- Finding the right researcher is key.
- The gene function studies are often unattractive for basic scientists, because they are relatively risky to take on. It is important to connect the clinical relevance for these genes of interest. This could be done by demonstrating an aberration in transcriptional activity, protein level, etc.

Summary:

- Challenges include funding. Need more funding for mechanistic studies if increase emphasis.
- UDN should have synergies and interactions both within centers and between centers.
- Many individuals are often the first presentation of their particular rare disease.

Q6 - Moving the UDN Forward (*Framer: David Eckstein. Perspectives: Rizwan Hamid and Bruce Korf. Moderator: Maren Scheuner.*)

What are the end goals for the UDN? What can the UDN uniquely do? What is the vision/mission? What is the best strategy to optimize the outcomes from the UDN in both clinical evaluation and discovery (diagnoses and research)? How will the UDN be sustained without CF support and how do we get there? What is the advantage of being a network?

End Goals:

- Sequencing newborn genomes may lead to fewer undiagnosed diseases with genetic bases. Limitations include lack of insurance coverage for exome or genome sequencing.
- Undiagnosed diseases research would benefit from developing a broader network with larger centers of excellence and including other researchers who are doing similar work. There may also be opportunities to bring them on as collaborators, allowing them to leverage the cores (e.g. sequencing, model organisms).
- Export UDN methodology and maybe limit taking on more roles that are beyond the scope.
- The UDN should study implementation across all sites and look at how things change with variability across sites. Are there general policies that work across the network? What successful attributes are contingent upon time and location?
- Next cycle should be improvement on current goals and long-term viability, bringing in a lot of new things may hurt long-term viability.

What can UDN uniquely do?:

- Focus on exporting methodology versus taking on new roles.
- Highlight the utility of using model organism data, even with a small sample size
- The UDN needs to be able to get the data out to the community. Clinical sites should be able to share a minimal data set to establish the effectiveness of the network.
- UDN success is contingent upon replicating itself in the general research/clinical communities.
- Ideas for other potential cores include: an Electron Microscopy Core, and a Stable Isotope Core for metabolic studies.

Sustainability of the UDN:

- Establish and record metrics that demonstrate value of the deep phenotyping process.
- Access to core resources would catalyze research endeavors. Build a strategy by which external researchers can leverage UDN data/services.
    - Core support is very limited with current UDN funds
- Look to other resources to fund clinical care of patients to ensure the availability of funds for the fundamental research portion of the project.

- By employing a diverse team of experts, one university was able to establish the cost effectiveness of ending the diagnostic odyssey. Because the economic rationale was demonstrated, a hospital now pays for these services.
- Challenges were described for throughput for a high depth phenotyping program due to the lack of an intensive one-week clinical work-up.
- The UDN should consider a model similar to the Comprehensive Cancer Center designation.

Vision/Mission:

- Need to consider difference rare undiagnosed versus unknown disease.
- The focus of the UDN should remain on the diagnosis of patients.
- UDN can help establish a paradigm for diagnosis.
- Don't have experience to change UDN goals yet, next 5 years aim to refine, need more data.
- Continue hybrid research/clinical model.

Panelist Discussion Summaries

David Flannery

- Payers want to know the clinical utility of genetic testing. Clinicians can do this by demonstrating improved patient outcomes via controlled trials, but this is likely not possible within the scope of the UDN.
- Payers would like clinicians to track various types of outcomes, including benefit to family members that is associated with genetic testing, and the impact that management of care has on a patient.
- The UDN may want to develop best practices guidelines on diagnosing undiagnosed patients.

Irene Maumenee

- As many as ¼ - ⅓ of genetic diseases are purely ocular or systemic with ocular involvement. Much like cases in the greater undiagnosed diseases community, ocular diseases are frequently mis-, under-, or undiagnosed. Many of these cases may in fact be unrecognized diseases.

Paul Melmeyer

- The NORD can help publicize the UDN. Very few undiagnosed patients know about the UDN and NORD would eventually like to fully publicize the UDN.
- NORD has been participating with multiple international organizations to establish an international consortium of patient advocacy organizations.
- NORD Patient Assistance program is only a temporary solution to funding genetic testing. Need to develop more long-term sustainable solutions for funding patient care.
- Great support for UDN in the community, want to see continue.

Wendy Chung

- The UDN should focus on what happens beyond the diagnosis. Yields need to be measured empirically.
- The UDN's value to the community stems from the network's ability to explore cutting edge, high risk challenges, such as implementation of exome versus genome sequencing. The UDN may want to consider scaling this up to more patients in order to start seeing patterns and yields.
- The UDN needs to ensure data sharing is accessible to multiple communities. dbGaP is a database with high barriers of access and not a complete solution.
- Assess the value of the cores (e.g. metabolic analysis, functional studies). Even with increased funds, functional studies remain a rate-limiting step.

Discussion

- Integrate deep phenotyping with cutting edge science. It will be important to have data drive the best clinical management strategies for the UDN.
- Advertising the network should be a programmatic priority. Reviewing applications is not too labor-intensive and casting as wide a net as possible is invaluable. Contacting professional organizations is a potential next step. Many potential referring physicians are unaware of the UDN.

Prioritizing Opportunities and Workshop Recommendations (*Anastasia Wise*)

What are the best opportunities/justifications for continuing the UDN into phase II? What should be emphasized? What can be deleted? What should be added? What opportunities should be prioritized?

Q1 - Intensive Clinical Evaluation

- Genotype first versus phenotype first, what is the best practice?
    - Need to make sure all the data are captured, need phenotype data even if genotyping comes first
    - Best practices will likely depend on clinical, financial, and location-based needs of the patient
- Collect environmental, historical, and epigenetic data and consider potential interactions, but be wary of small sample size
- Should there be a reasonable minimum core dataset across network, some standard phenotyping and uniformity
    - Recognizing patterns in the data will be important for improving diagnosis
- Focused expertise has pros and cons. Patients should have a local workup prior to their visit to the UDN Clinical Sites

Q2 - Transitions of Care

- Primary mission of the UDN will be diagnosis, but the group will need to consider impact beyond mission, and how the process changes the life of a patient
    - Currently isolated from clinical care practice
    - Translate to clinical setting
    - Research utilization, leveraging collaborative networks

- The UDN will need to develop a standard plan for what happens next (e.g., re-contacting patients, collaborating with outside clinicians for long term care)
- Capture, evaluate, and refine UDN patient diversity
- Leverage existing resources

Q3 - Patient and Family Partnership

- Study patients' and families' psychological perspectives
    - How do we classify and better support patients and their families? It may be helpful to engage with families sooner in the clinical evaluation
- Clinicians need to set clear patient expectations
- Create a patient advisory group
- Partner with NORD and other support groups to develop a patient mentorship model
- Advertise the services that the UDN provides.
- Patient to patient communication is an important avenue for patient engagement.

Q4 - Training, Sharing & Collaborations

- More training needed
    - Expand outside UDN, blueprint and establish how much support external collaborators might need
    - New expertise
    - Curriculum development
- Increase collaborations
    - Bringing in health care providers
    - International collaborations for case matching, data sharing and identification of ethnic-specific variants
    - Have patients collaborate with organizations that will match funds
- Explore opportunities to connect data
- Increase funding for functional studies
    - Attendees cited the value of a model where the government publishes a gene list and awards small grants (~$25K) to investigators who already specialize in that gene.

Q5 - The Virtuous Cycle and Integrating Data

- Emphasis should also be placed on treatment, not just diagnosis
- Challenges for funding
    - Need more funding for mechanistic studies
- UDN model should have synergies and interactions within and between centers
- Finding the right researcher is key

Q6 - Moving the UDN Forward

- The NIH will need to think about how to fund the UDN during and after a second phase.
- Develop practices for patient follow-up
- Keep access to current UDN cores. New cores may be difficult to fund.
- Develop ways for other clinical sites to access and collaborate with the UDN.
- Mechanistic studies should be considered a part of diagnosis