Unmet Medical Device Needs
for Patients With Rare Diseases

NIH National Center for Advancing Translational Sciences

FDA U.S. FOOD & DRUG ADMINISTRATION

CONTENTS

APPENDICES

Background

The impact of rare diseases is likely far greater than the term implies. The lives of nearly 30 million Americans, half of whom are children, are directly affected by approximately 7,000 rare diseases.[1] Statistics for the number of people seeking care with disorders of unknown or unclear etiology (i.e., undiagnosed rare disease patients) remain elusive. When these potential numbers are considered alongside known numbers, the probability that every health care professional in the United States cares for at least one patient with a rare disease—knowingly or unknowingly—becomes a relevant consideration for resource allocation and policy development within the U.S. health care ecosystem.

The U.S. Food and Drug Administration (FDA) and the National Center for Advancing Translational Sciences (NCATS)/Office of Rare Diseases Research (ORDR) at the National Institutes of Health (NIH) sought to better understand the medical device needs of patients with rare diseases. Medical devices represent a highly diverse spectrum of promising technologies for rare diseases, both in diagnostic testing options and in treatments. These technologies range anywhere from simple medical instruments to cutting-edge scientific advances in implants and nanotechnology.

The Orphan Drug Act generally defines a rare disease as one affecting fewer than 200,000 people in the United States, yet many rare diseases affect only tens to hundreds of people. This level of rarity adversely affects the potential for improving diagnostic and therapeutic options to better serve this population. In the past three decades, the Orphan Drug Act has stimulated a significant increase in the development of drugs and biologics for these diseases; however, development of devices for rare diseases has lagged behind.

From late 2015 to 2016, FDA and NCATS/ORDR at NIH conducted a needs assessment to better understand unmet medical device needs for rare diseases; generate meaningful data to inform patients, practitioners, policymakers, and device developers on the needs, barriers, and incentives related to medical device development for rare diseases; and increase public awareness of these needs. The assessment included a subfocus on pediatric rare disease patients. This report describes the results of that assessment, which offers key findings about device needs in adult and pediatric rare disease populations.

Methods

The agencies conducted an online survey of four clinician groups that advise or work with FDA concerning device development or with NCATS regarding clinical trials of rare diseases. Two of these groups consisted of clinicians focusing on pediatric product issues, which provided a better understanding of the unique needs of pediatric patients. The complete clinician groups included physicians and non-physicians with patient experience (e.g., dentists, optometrists, and therapists). In this report, those who responded to the survey from the clinician groups are referred to as respondents or clinicians.

The survey was designed to elicit information regarding (1) satisfaction with current diagnostic and therapeutic devices, (2) unmet diagnostic and therapeutic device needs for specific rare diseases identified by each respondent, (3) unmet diagnostic and therapeutic device needs for rare disease populations in general, (4) impediments to medical device development, and (5) familiarity and

[1] Global Genes. *Rare diseases: Facts and statistics*. 2015. http://globalgenes.org/rare-diseases-facts-statistics/. Accessed January 21, 2017.

experience with Humanitarian Use Devices (HUDs). Those with direct experience were also asked about current diagnostic and therapeutic practices for specific rare diseases they identified, including limitations in current practices. For a companion manuscript, a separate statistical analysis was performed on results solely from participating physicians who had direct experience with or knowledge of rare diseases and the results of that analysis will be published soon. There was no intent to prioritize needs by disease or to emphasize needs in one population over any other.

Survey Respondents

In total, 1,342 clinicians received the survey, including 1,154 physicians and 188 non-physicians (827 members of the FDA Center for Devices and Radiological Health Advisory Committee,[2] 26 members of the FDA Pediatric Advisory Committee,[3] 63 members of the FDA Pediatric Device Consortia,[4] and 426 members of the NCATS/ORDR Rare Diseases Clinical Research Network program).[5] In total, 588 completed the survey, for a response rate of 44 percent. The respondents reported expertise covering many specialties, and 33 percent had a pediatric focus (a pediatric specialty or significant experience with pediatric patients). A large majority (90 percent) reported they had direct experience diagnosing or treating patients with rare diseases or had knowledge of rare diseases. Of those with direct experience, 93 percent had seen such patients in the past two years.

Findings

The survey results clearly documented that patients with rare diseases face numerous unmet needs related to diagnostic and therapeutic devices. In addition, device needs of pediatric patients sometimes differ from those of adults. For example, devices must be able to grow with a child, be modified to a smaller size, or be less invasive. Overall, respondents believed that creating entirely new devices is what is most needed, rather than modifying existing devices or repurposing devices for other indications. The limitations of existing diagnostic devices included their lack of sensitivity and specificity and their cumbersome and invasive nature. Respondents noted that meeting therapeutic device needs would improve care for patients across all types of rare diseases. However, the costs of research and development, lack of profitability for industry, and challenges of conducting trials in small, heterogeneous populations stand in the way of progress in this area. Notably, genetic tests are essential tools necessary for the diagnosis and treatment of many rare conditions, and the critical shortage of such tests was mentioned repeatedly by survey respondents. Overall findings from physician respondents were similar to those from non-physician respondents.

[2] For more information about the Center for Devices and Radiological Health, visit https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH
[3] For more information about the Pediatric Advisory Committee, visit https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/
[4] For more information about the Pediatric Device Consortia grant program, visit https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/PediatricDeviceConsortiaGrantsProgram/
[5] For more information about the Rare Diseases Clinical Research Network, visit https://ncats.nih.gov/rdcrn

Key Findings

- **Clinicians overwhelmingly cited multiple needs for new or improved medical devices for diagnosing and treating rare diseases**

461 unique rare diseases were cited with 917 specifying unmet device needs
91% believed a new or improved device is needed
64% were dissatisfied with existing diagnostic and/or therapeutic devices

- **There is a critical need for entirely new devices rather than modifying or repurposing devices, which are often inadequate**

77% cited a need for an entirely new diagnostic and/or therapeutic device
23% cited a need for only modified or repurposed diagnostic and/or therapeutic devices

- **Existing devices have several limitations in diagnosing or treating rare diseases**

79% reported diagnostic devices for genetic disorders as an unmet need
37% currently repurpose an FDA-approved therapeutic device

- **Several impediments to developing new devices for rare diseases were mentioned**

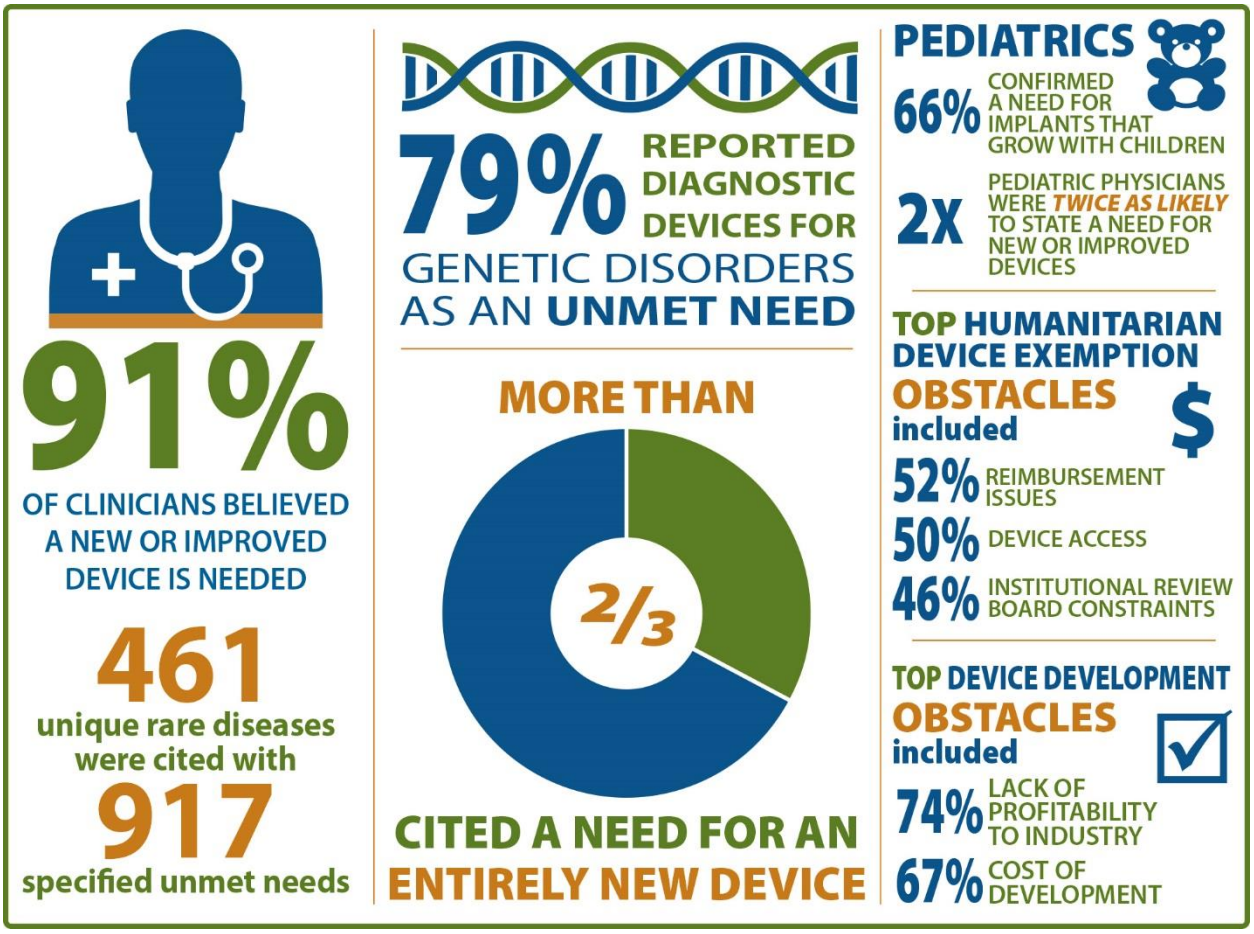
74% saw the lack of profitability to industry as a large impediment
67% saw the cost of development as a large impediment

- **The Humanitarian Device Exemption (HDE) provides a helpful pathway for bringing devices to market, but there are obstacles to its use.**

Top challenges cited by the 51% of respondents reporting familiarity with HUD/HDEs include the following:
52% said reimbursement
50% reported gaining access to HDE devices
46% indicated institutional review board constraints

- **While there are unique pediatric challenges, respondents with pediatric experience reported high levels of dissatisfaction similar to those without pediatric experience**

33% of clinicians had a pediatric focus
66% believed there is a pediatric need for implants that grow along with the child
44% confirmed intrathecal ports for drug delivery as a pediatric need



In summary, this national survey of government-associated clinicians verifies the need to develop devices for rare diseases and highlights the uniqueness of subpopulations. As described in the conclusion of this report, FDA and NIH provide programs to address these issues that encourage the development of devices for unmet medical device needs, as well as incentive programs that provide funding for the clinical development of products. Sustained support of the medical device ecosystem will accelerate the development of critically needed devices for rare diseases, thereby enhancing care options for these vulnerable patients.

Unmet Device Needs in Rare Diseases

The U.S. Food and Drug Administration (FDA) and the National Center for Advancing Translational Sciences (NCATS)/Office of Rare Diseases Research (ORDR) at the National Institutes of Health (NIH) sought to better understand the medical device needs of patients with rare diseases. As defined by the Orphan Drug Act (ODA), a rare disease is one affecting fewer than 200,000 people in the United States.[6,7,8] Under this definition, approximately 7,000 rare diseases have been identified to date. They affect an estimated 30 million Americans, approximately half of whom are children.[9] Rare diseases are responsible for 35 percent of deaths in the first year of life.[10] Because the patient populations for each of these diseases are relatively small (in many cases, as low as tens or hundreds of patients), they may be neglected or overlooked by clinicians, the research community, and those who invest in medical research and device development, resulting in unmet diagnostic and therapeutic needs for patients.

Since they are so rarely seen and often difficult to diagnose, patients with a rare disease may search for a diagnosis for years. According to NIH, as many as 80 percent of rare diseases are genetic in origin, often requiring genetic testing to diagnose.[11] If diagnosis is delayed, symptoms can advance beyond the point that care will be optimal. Delayed diagnosis can lead to delays in intervention and patient care, which in some cases may contribute to premature death. According to the Institute of Medicine report, *Rare Diseases and Orphan Products: Accelerating Research and Development*: "The diagnosis of many rare diseases has been limited historically by imprecise, cumbersome, or expensive testing and by limitations on physician and patient access to the most up-to-date information about rare diseases (including diagnostic criteria) and other diagnostic resources."[12,13]

In addition, patients with a rare disease often seek treatment in clinics where the condition, whether diagnosed or not, has never been seen before. Treatment—when available—can be elusive, especially for the lowest prevalence disorders, and can encompass a wide variety of approaches, including medication, nutrition, surgery, and medical devices. The Institute of Medicine report

[6] Genetic and Rare Diseases Information Center. FAQs about rare diseases. https://rarediseases.info.nih.gov/about-gard/pages/31/frequently-asked-questions. Accessed January 21, 2017.

[7] Drugs intended for diseases or conditions affecting 200,000 or more people, or vaccines, diagnostic drugs, or preventive drugs to be administered to 200,000 or more persons per year in the United States are also eligible for this definition if there is no reasonable expectation that costs of research and development of the drug for the indication can be recovered by sales of the drug in the United States, as specified in 21 CFR 316.21.

[8] The ODA definition of rare disease differs from the one used for the Humanitarian Device Exemption (HDE) program. The HDE program created an alternative pathway for getting market approval for medical devices to help people with rare diseases or conditions. The HDE program includes those diseases or conditions affecting fewer than 4,000 individuals in the United States annually and is thus a much narrower scope than those defined in the ODA. The 200,000-prevalence definition was used for this survey to gather data on a wider range of rare diseases.

[9] Global Genes. *Rare diseases: Facts and statistics.* 2015. http://globalgenes.org/rare-diseases-facts-statistics/. Accessed January 21, 2017.

[10] Global Genes, *Rare diseases: Facts and statistics*.

[11] Institute of Medicine. *Rare diseases and orphan products: Accelerating research and development.* Washington, DC: The National Academies Press. 2010.

[12] Institute of Medicine, *Rare diseases and orphan products.* 59.

[13] In vitro diagnostic tests are regulated by FDA as devices. In this report, the term diagnostic device is used to include such diagnostic tests.

noted that "for rare diseases, efforts to accelerate research and product development clearly focus on drugs and biological products. Devices and the need for devices are much less frequently mentioned in journal articles or stakeholder conversations. When devices for rare conditions are discussed, it is generally in connection with pediatric populations."[14] Device development for rare diseases significantly lags behind orphan drug development. In the past three decades, the ODA has stimulated a significant increase in drug and biologic development for these diseases.[15] Even so, patients with rare diseases may face unmet needs that can be exacerbated not only by the lack of effective drugs but also by a lack of medical devices for both diagnosis and treatment.[16]

Finally, as noted, approximately half of rare diseases affect children, and they can be serious, disabling, and life-threatening. Individuals with a rare disease can experience shortened life expectancy or decreased quality of life; thus, developing or improving medical devices that can be used in the pediatric population is critical. While this report focuses on device needs across the general rare disease population, it also focuses on issues specific to the pediatric population.

Purpose of This Needs Assessment

In the past decade, increased attention given to rare diseases—resulting from the ODA, advancing science and including precision medicine, as well as from heightened interest in the patient advocacy community—has highlighted the need to better document and meet medical device needs for rare diseases. Both the Institute of Medicine report and a 2011 FDA report to Congress on rare and neglected diseases[17] recommended an assessment of unmet medical device needs for patients with rare diseases. The FDA report also recommended an assessment of "the barriers to, and meaningful incentives for, the development of medical devices for rare diseases."[18]

In late 2013, FDA and NCATS/ORDR at NIH partnered to elicit feedback and guidance on conducting an assessment to address device needs for patients with rare diseases. Specifically, they sought to:

- Better understand unmet medical device needs for rare diseases.
- Generate meaningful data to inform patients, practitioners, policy makers, and device developers on the needs, barriers, and incentives related to medical device development for rare diseases.
- Increase public awareness of these needs.

---

[14] Institute of Medicine, *Rare diseases and orphan products*, 59.

[15] Braun, MM, Farag-El-Massah, S, Xu, K, Coté, TR. Emergence of orphan drugs in the United States: A quantitative assessment of the first 25 years. *Nature Reviews Drug Discovery*, *9*(7), 519–22. 2010. doi: 10.1038/nrd3160

[16] According to the FDA, a medical device is "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is: recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them; intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or; intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes."

[17] U.S. Department of Health and Human Services, FDA. *Report to Congress: Improving the prevention, diagnosis, and treatment of rare and neglected diseases.* March 2011. http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM266374.pdf. Accessed January 21, 2017.

[18] FDA, *Report to Congress,* 7.

To address the large proportion of pediatric patients with rare diseases, the assessment included a subfocus on pediatric medical device needs. This report describes the results of that effort and offers key findings about unmet device needs in adult and pediatric rare disease populations.

For the purposes of this survey, an unmet medical need exists when there are no approved devices for the treatment or diagnosis of a disease or condition, or when a novel device could provide a clinically meaningful advantage over existing approved devices.

The purpose of this assessment was to document and raise awareness of the need for medical devices for rare disease patients. It is anticipated that, as a result, policy makers, funding agencies and investors, device developers, clinicians, and patient advocacy groups will become more aware of medical device needs for rare disease patients and will use the information presented here to accelerate the development of medical devices for this patient population.

Stakeholder Consultations

To conduct the needs assessment, FDA's Office of Orphan Products Development (OOPD), Center for Devices and Radiological Health (CDRH), and Office of Planning, together with NCATS/ORDR, formed a Needs Assessment Working Group (NAWG). The NAWG planned a collaborative effort to reach out to various rare disease and pediatric stakeholders, including researchers, clinicians (including physicians and non-physician clinicians who work with patients), patients, patient advocacy organizations, and members of industry. Besides FDA and NCATS/ORDR staff, stakeholders from the American Academy of Pediatrics, the American Medical Association, the National Organization for Rare Disorders, and AdvaMed participated in a project kickoff meeting on Oct. 30, 2013. At the meeting, the agencies solicited experts and stakeholders to discuss project goals, desired outcomes, key objectives, approaches to obtaining data, and complexities and obstacles. These stakeholders were also invited to provide additional input to the NAWG to guide the project. On Jan. 8, 2014, FDA held a public workshop titled "Complex Issues in Developing Medical Devices for Pediatric Patients Affected by Rare Diseases." During this workshop, the NAWG provided an overview and solicited feedback on the medical devices for rare diseases needs assessment project. Input from stakeholders and public attendees during and after the meeting informed and focused NAWG's approach to the needs assessment.

Survey Methodology

After these stakeholder consultations and consideration of a number of factors, including available resources, the NAWG decided to conduct an online survey of four clinician groups whose members were directly accessible and generally had experience or knowledge in the areas of medical devices and/or rare diseases. To better understand and address the unique needs of pediatric patients, two of the selected groups included clinicians with predominant training and experience with pediatric patients. The surveys were administered to 1,342 clinicians, including 827 clinicians associated with the FDA CDRH Advisory Committee, 26 representatives of the FDA Pediatric Advisory Committee (PAC), 63 members of the FDA Pediatric Device Consortia (PDC), and 426 clinicians associated with the NCATS/ORDR Rare Diseases Clinical Research Network (RDCRN) program. Of these individuals, 1,154 were physicians, and 188 held other credentials; the non-physicians primarily held doctorates and worked in the area of rare diseases. Following are brief descriptions of these groups.

- **FDA CDRH Advisory Committee.** This committee is made up of 18 panels primarily consisting of expert physicians and other clinicians who provide advice to the FDA about issues related to the safety and effectiveness of medical devices.
- **FDA PAC.** This committee, primarily consisting of expert physicians, advises and makes recommendations to the FDA on a variety of pediatric issues and concerns, including research priorities; ethics, design, and analysis of clinical trials; and labeling disputes or changes in labels.
- **FDA PDC.** The consortia includes physicians and other experts in medical device development who work together to promote the development of medical devices for children.
- **NCATS/ORDR RDCRN.** The RDCRN program provides support for clinical studies and facilitates collaboration, study enrollment, and data sharing to advance research on rare diseases. Through its network, physician scientists and their multidisciplinary teams work

with representatives of patient advocacy groups to advance rare disease clinical research and investigate new treatments for patients.

The survey included closed and open-ended questions and solicited information on both diagnostic and therapeutic needs. All respondents with experience with rare disease patients or knowledge of rare diseases were asked about (1) satisfaction with current diagnostic and therapeutic devices, (2) unmet diagnostic and therapeutic device needs for up to three specific rare diseases identified by each respondent, and (3) unmet diagnostic and therapeutic device needs for rare disease populations in general. Those with direct experience with rare disease patients were also asked about current diagnostic and therapeutic practices for specific rare diseases identified by each respondent. In addition, the survey included questions that could be answered by all respondents, regardless of their experience with rare disease populations, that focused on potential benefits of increased medical device development and testing, impediments to such activities, and familiarity and experience with HUDs. Finally, all respondents were asked about their clinical background and experiences, including the number and types of patients seen, clinical specialty, setting(s) for care, years of clinical experience, and involvement in the development of a medical device and/or medical device trials.

Prior to fielding the survey questionnaire, cognitive testing was conducted with nine physicians whom NAWG identified to ensure clarity in the survey questions, question order, and instructions. Once the survey questionnaire was programmed, the NAWG tested it with FDA physician employees. The survey also was piloted with a subset of the respondents from the FDA CDRH Advisory Committee before being administered to all groups. The final survey, containing 50 questions, can be found in Appendix A.

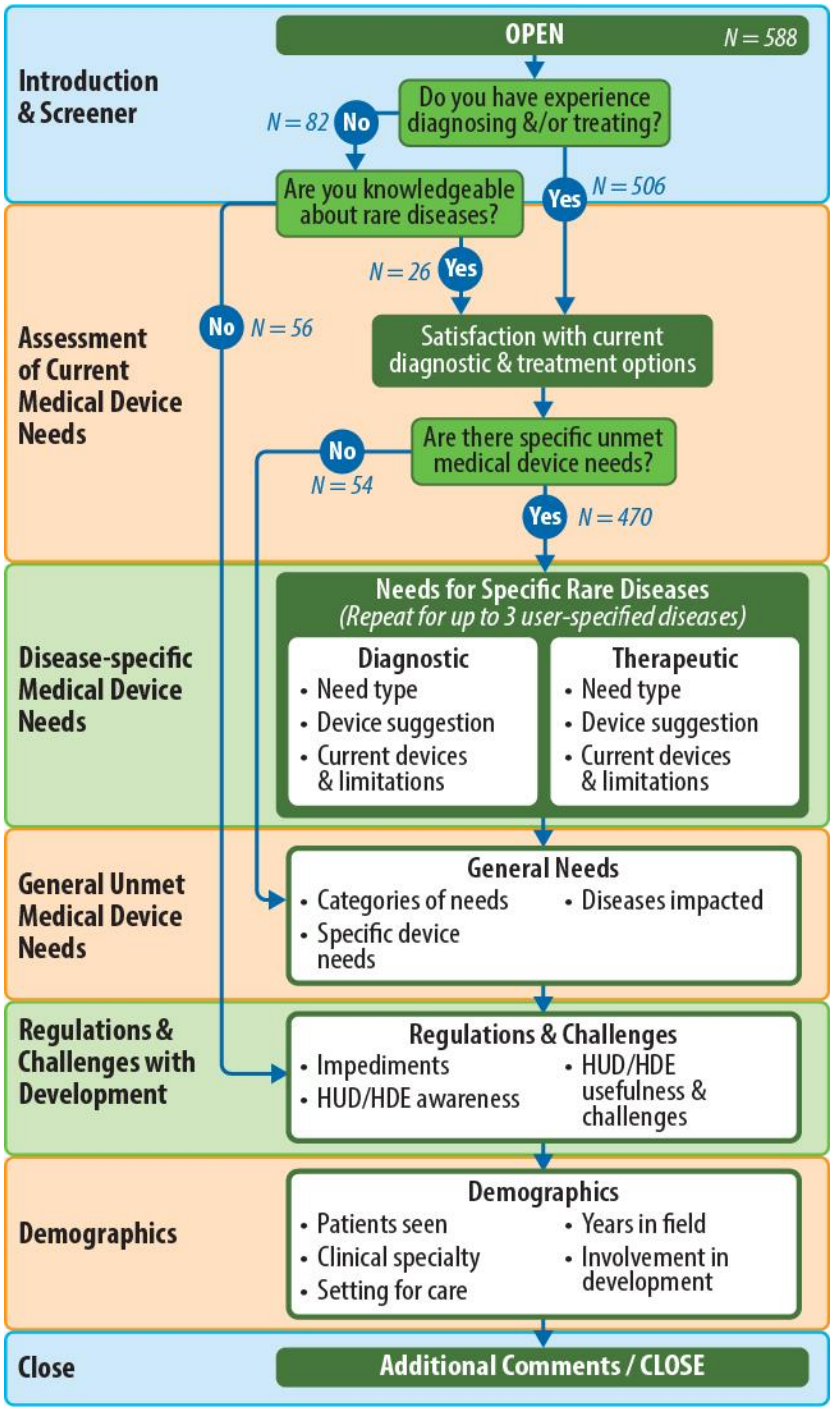
FDA and its contractor, ICF, independently sought and received Institutional Review Board (IRB) approval before fielding the survey. The FDA CDRH Advisory Committee survey opened Nov. 4, 2015, and closed Dec. 5, 2015. The FDA PAC, FDA PDC, and NCATS/ORDR RDCRN survey opened Jan. 28, 2016, and closed Feb. 29, 2016.

In total, 1,342 people were successfully invited to participate (that is, although 1,381 individuals were invited, 39 invitations bounced back), of whom 588 completed the survey in whole or in part,[19] for a response rate of 44 percent. Of note, most questions in the survey could be skipped, so the sample size (N) for each survey question varied on the basis of both the skip patterns and the ability of respondents to skip the question. For this reason, we present the sample size of respondents for the questions throughout the report.

Figure 1 illustrates the survey organization and primary skip patterns, as well as the number of respondents who responded to each section of the survey. For each skip pattern shown, the number of respondents who were skipped into or out of a given section is shown to provide a better understanding of how many clinicians responded to each section of the survey.

[19] To be considered a completed survey, respondents with direct experience with rare disease populations or knowledge of rare diseases must have completed the applicable diagnostic and/or treatment-related questions for at least one rare disease, leaving no more than one question blank in each series. For those without direct experience or knowledge, respondents must have completed all applicable survey questions to be considered complete. To be considered a partially completed survey, the respondent must have completed the opening screener question(s) about direct experience with rare disease populations and knowledge of rare diseases, plus at least one applicable survey question on the needs of medical devices for rare disease. A full description of how the determination of a wholly or partially completed survey was made is available in Appendix B.

Figure 1: Survey Organization and Skip Patterns



Data Analysis

Details about the data preparation and analysis can be found in Appendix B. However, a few aspects are worth noting here.

- Although responses were captured separately from those with direct experience diagnosing or treating patients with rare diseases and those with knowledge of rare diseases, the responses from both groups were similar throughout. The group of respondents with knowledge but not direct treatment experience was small. Because of this, the data for the two groups of respondents were combined and are reported together throughout this report. However, those without direct experience were not asked questions about current diagnostic and therapeutic practices.
- For the survey items covering unmet medical device needs for user-specified rare diseases, respondents were asked to enter the names and answer questions related to up to three rare diseases, in order of greatest need. Respondents were required to answer only the questions for the first disease they entered and were given the option to skip the related questions for the second and third diseases they named, so the sample size for responses varies. The analysis for these questions occurred at the disease level rather than the respondent level to ensure that all diseases were analyzed together rather than entering separate analyses for the first, second, and third diseases.
- Prior to the analysis, the NAWG reviewed the list of user-specified rare diseases to ensure that the diseases may qualify as rare diseases under the definition used for the survey (a disease or condition with a prevalence of fewer than 200,000 persons in the United States). The device suggestions provided by the respondents for the disease were reviewed, in addition to the disease name, to ensure that a disease not generally fitting the rare disease definition but possibly having features that would limit the usage of the device to a subset of patients would be categorized appropriately. Similarly, FDA categorized rare diseases and general device needs according to the related medical specialties.
- Separate analyses of respondents with a pediatric focus (those who had a pediatric specialty or significant experience with pediatric patients) were conducted to examine differences among this key group of interest compared to all respondents. Where notable differences occurred, they are presented throughout this report. In total, 33 percent of respondents (N=192) were included in the category of clinicians with a pediatric focus. Two survey items were used to distinguish clinicians with a pediatric focus. The first asked respondents to indicate their clinical specialty. Eighty-nine respondents (15 percent of all respondents) selected the pediatrics category for the clinical specialty question.[20] A second question was asked only of those respondents who had seen rare disease patients during the previous two years; respondents were asked to specify the proportion of their patients over the previous two years who were age 21 or younger. In response to this question, 179 respondents (30 percent of all respondents) indicated that half or more of their patients were 21 or younger. Respondents were considered clinicians with a pediatric focus if they met at least one of these two criteria. In total, 76 respondents met both criteria, 13 respondents reported

[20] In five cases, respondents were assigned to the pediatrics category on the basis of open-ended responses they provided when selecting "other" for their clinical specialty. For example, a respondent who entered "pediatric cardiology" was re-assigned to the categories of cardiology and pediatrics.

they had a clinical specialty in pediatrics, and 103 respondents reported that half or more of their patients were pediatric but did not report a clinical specialty in pediatrics.

Appendix B provides a more complete description of the methodology. Results are descriptive only, and no statistical analyses or formal comparisons were conducted for the results presented in the report.

Survey results are presented in the following order: Section A provides information about the specialties and clinical experience of the survey respondents; Section B reports survey findings regarding satisfaction with existing devices; Section C reports results from questions about cross-cutting needs of all rare disease populations; Section D reviews the survey findings on current diagnostic and treatment practices and satisfaction with those practices and discusses unmet medical device needs for specific rare diseases; and Section E reports results from a series of questions about impediments to the development of medical devices for rare diseases, as well as respondent experiences with the HUD/HDE regulatory pathway.

A. Description of Survey Respondents

Respondents were asked about their medical specialty, experience treating patients (including pediatric patients), practice setting, years of practice, and involvement in medical device trials or development. Most had clinical experience with rare diseases and with pediatric populations, largely in the academic medical setting. A majority also had experience with device development and/or testing.

Among the 446 respondents who reported their clinical specialty, more than 39 clinical specialties were represented. These were grouped into two overarching categories using the clinical training approach: Surgery and Medicine/Non-surgery, as shown in Figure 2. Respondents were assigned to the Surgery category if they identified any of the following specialties: Colon and Rectal Surgery, Neurological Surgery, Orthopedic Surgery, Otolaryngology, Plastic Surgery, Surgery, Thoracic Surgery, Urology, Obstetrics and Gynecology, or Ophthalmology. Respondents who did not check any of these but checked a different specialty were assigned to the Medicine/Non-surgery category. Table 1 shows the composition of these three overarching categories.

Figure 2: Clinical Specialties of All Respondents (N= 459)

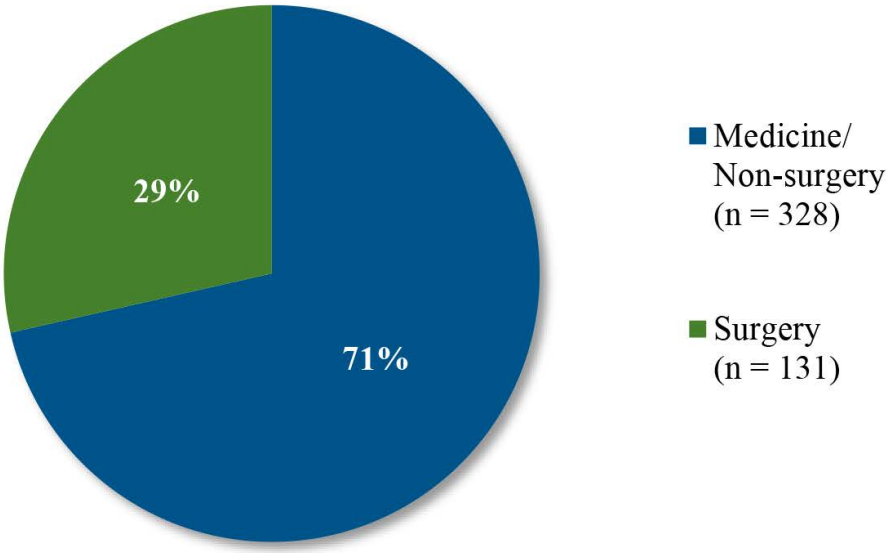


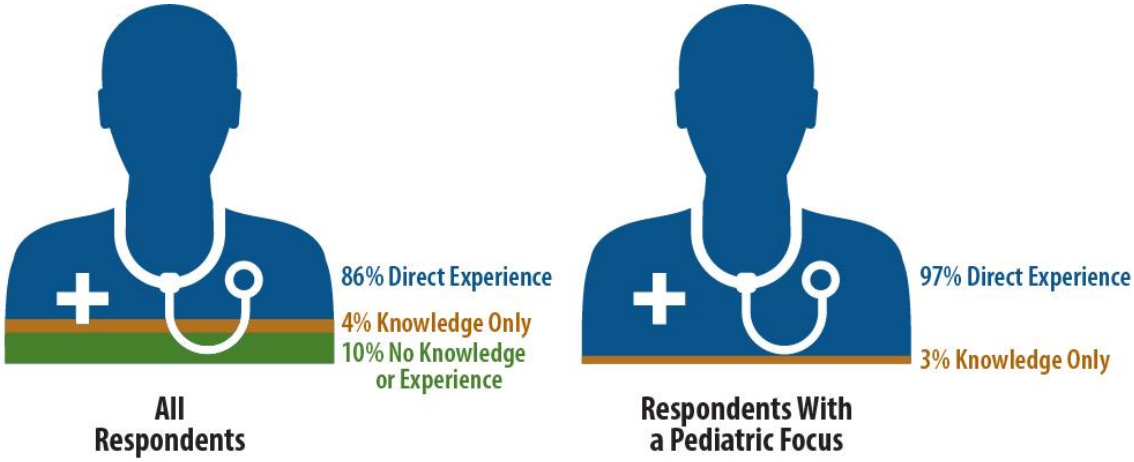
Table 1: Clinical Specialties of Respondents

All Respondents (N = 459)		Pediatric Respondents (N = 191)	
Clinical Specialty	Frequency (#)	Clinical Specialty	Frequency (#)
Pediatrics	89	Pediatrics	89
Neurology	53	Neurology	25
Pulmonology	39	Medical Genetics	20
Cardiology	33	Cardiology	18
Ophthalmology	31	Pulmonology	13
Medical Genetics	26	Surgery	10
Internal Medicine	25	Nephrology	10
Orthopaedic Surgery	24	Oncology	9
Gastroenterology	21	Allergy and Immunology	8
Surgery	21	Internal Medicine	8
Oncology	20	Orthopaedic Surgery	7
Radiology	20	Gastroenterology	7
Pathology	17	Ophthalmology	7
Nephrology	16	Thoracic Surgery	6
Otolaryngology	16	Endocrinology	6
Allergy and Immunology	12	Pathology	5
Neurological Surgery	12	Otolaryngology	4
Thoracic Surgery	12	Neurological Surgery	4
Endocrinology	9	Obstetrics and Gynecology	3
Obstetrics and Gynecology	8	Psychiatry	3
Plastic Surgery	7	Radiology	2
Psychiatry	7	Plastic Surgery	1
Rheumatology	5	Rheumatology	1
Urology	5	Urology	1
Physical Medicine and Rehabilitation	4	Physical Medicine and Rehabilitation	1
Geriatrics	3	Geriatrics	1
Anesthesiology	2	Anesthesiology	1
Dermatology	2	Nuclear Medicine	1
Diagnostic Radiology	2	Physiatry	1
Nuclear Medicine	2	Preventive Medicine	1
Colon and Rectal Surgery	1		
Physiatry	1		
Preventive Medicine	1		
Emergency Medicine	1		

* Respondents were able to select multiple clinical specialties. This table represents each selected specialty except the "Other, specify" category. Thus N will sum to greater than the 459 respondents who reported their clinical specialty.

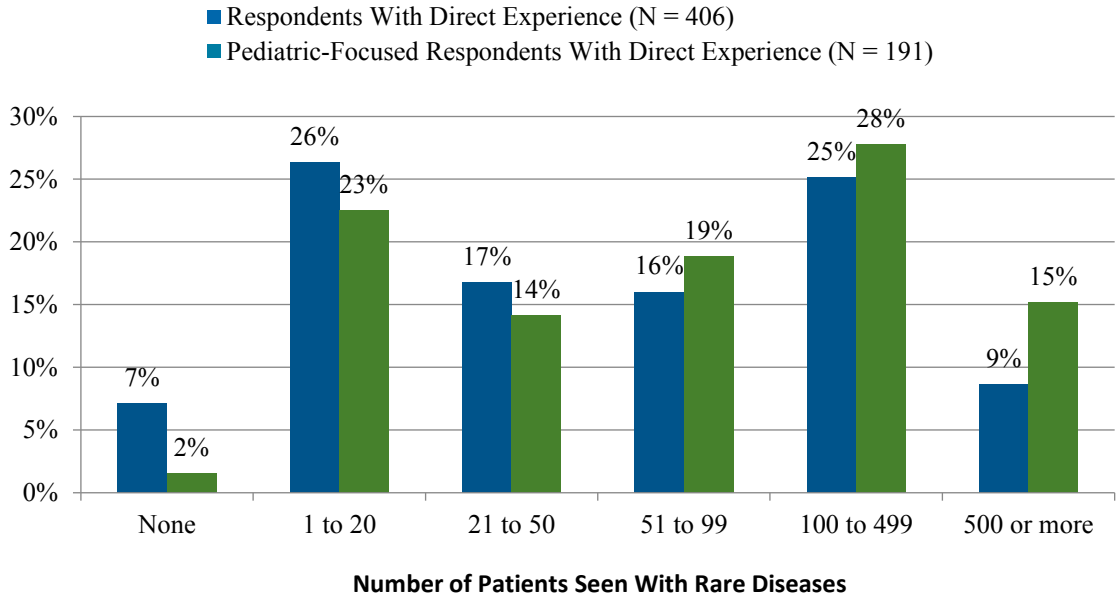
As Figure 3 shows, a large majority (86 percent) of the total respondents reported they had direct experience diagnosing or treating patients with rare diseases. The remaining respondents either had knowledge of rare diseases but no direct experience with rare disease patients (4 percent) or had neither experience nor knowledge (10 percent). Nearly all (97 percent) of the respondents with a pediatric focus had direct experience with rare disease patients.

Figure 3: Rare Disease Experience of Survey Respondents



Respondents with direct experience were asked about the number of patients with rare diseases they had seen in the past two years and what proportion of those patients were 21 years old or younger. As illustrated in Figure 4, of the 406 clinicians who had direct experience and responded to this question, 377 had seen rare disease patients in the previous two years, although the volume of these patients varied across the clinicians.

Figure 4: Respondents' Experience With Rare Disease Patients Within Previous 2 Years



Most of the respondents (87 percent) had practiced in their field for more than 10 years. Furthermore, most respondents (83 percent of all respondents and 94 percent of those with a pediatric focus) practiced medicine in an academic clinical center, with 8 percent of all respondents and 3 percent of those with a pediatric focus involved in a group practice. While academic medical centers are generally considered important hubs of rare disease knowledge, one limitation of the survey data may be its lack of inclusion of clinicians who were not affiliated with an academic medical center.

Finally, 61 percent of all respondents (67 percent of respondents with a pediatric focus) reported past experience developing a medical device, and 57 percent of all respondents (55 percent of respondents with a pediatric focus) reported past involvement in conducting medical device trials. These percentages are likely higher than would be found in the general clinician population because the survey population was selected based on their associations with FDA related to device development or with NCATS regarding clinical trials of devices.

B. Satisfaction With Existing Devices

Overall, respondents were more dissatisfied with existing therapeutic devices than diagnostic devices.

- Thirty-six percent of respondents were dissatisfied with available *diagnostic* devices for rare diseases, compared to 44 percent who were satisfied. Among clinicians with a pediatric focus, 34 percent noted dissatisfaction and 51 percent indicated satisfaction with current diagnostic devices.
- Fifty-nine percent of respondents were dissatisfied with available *therapeutic* devices for rare diseases, compared to 17 percent who were satisfied. Among those representing a pediatric specialty, 62 percent indicated dissatisfaction with current therapeutic devices and 18 percent expressed satisfaction.

C. Device Needs Across Rare Diseases

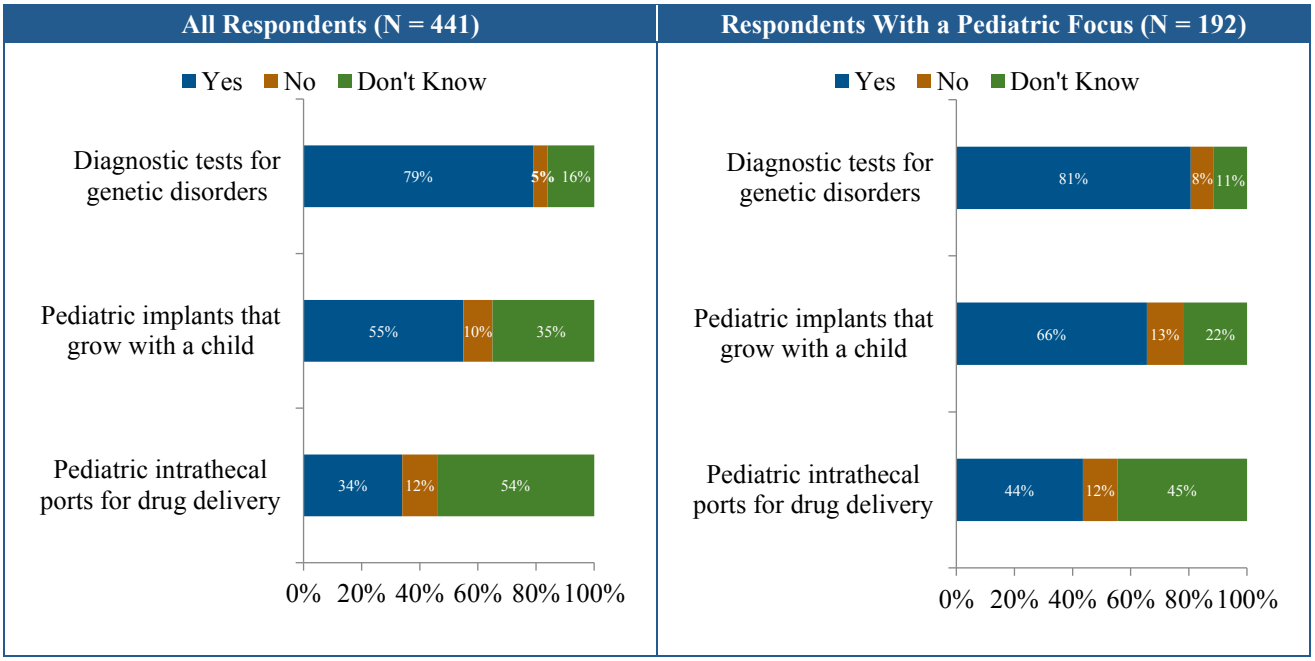
The survey aimed in part to assess the needs for those medical devices that may apply to more than one rare disease. A series of questions on this topic was asked of all respondents with either direct experience with rare disease populations or knowledge of rare diseases. Respondents were first asked about three specific categories of device needs and then three respondent-identified needs. Because respondents were able to enter between one and three needs, data for those questions were analyzed at the need level rather than the respondent level. The results clearly document that there are broad unmet device needs for patients with rare diseases for both diagnosis and therapy and that needs exist across adult and pediatric populations, in multiple settings, and across clinical areas.

Examples of General Device Needs Across the Rare Diseases

Respondents were given three examples of broad device categories—genetic tests, pediatric implants that grow with a child, and pediatric intrathecal ports for drug delivery—and asked whether they believed there were unmet needs for each. Results are shown in Figure 5, broken out by all 441 respondents who answered these questions and the 192 respondents with a pediatric focus who answered these questions. Of note, diagnostic tests for genetic disorders were seen as an unmet need by 79 percent of all respondents and 81 percent of respondents with a pediatric

focus. These high percentages were also reflected in respondents' suggestions for meeting diagnostic needs, which can be found in section D.

Figure 5: Needs for Specific Categories of Devices*



*These questions were asked only of respondents with direct experience or knowledge of rare diseases.

When respondents were asked further open-ended questions about general device needs that would have the greatest impact on rare disease patients, 47 responses referred specifically to the need for a genetic test. The need for genetic tests was also commonly mentioned in the open-ended questions about needs for up to three respondent-entered diseases. Table 2 illustrates some of the rare diseases identified by respondents as needing a new or better genetic diagnostic device. Appendix C provides a summary of all of the reported general device needs for new or improved devices, including those with a need for genetic tests.

Table 2: Sample Rare Diseases With Genetic Test Needs

Atypical hemolytic uremic syndrome	Inherited retinal dystrophies
Bone sarcomas	Jarcho-Levin syndrome
Craniofacial abnormalities	Jeune syndrome
Central apnea in newborns	Laminin deficiency
Charcot-Marie-Tooth disease	Larsen's syndrome
Congenitally inherited inborn errors of metabolism/acid oxidation defects	Lipodystrophy
Corneal dystrophies	Long QT syndrome
Cornelia de Lange Syndrome	Low-grade chondrosarcoma
Cystic fibrosis	Lynch syndrome
Ewing sarcoma	Malignant hyperthermia
Fabry disease	Maturity onset diabetes of the young
Familial exudative vitreoretinopathy	Muccopolysaccharidosis
Genetic causes of aortic dissection and aneurysm	Myocardial channelopathies
Genetic epilepsy syndromes	Pattern dystrophies of the retina
Genetic neurological disorders	Polycystic kidney disease
Granular corneal dystrophy	Pre-symptomatic muscular dystrophies
Heart failure with preserved ejection fraction	Rare genetic malabsorption disorders
Hereditary pancreatitis	Rare kidney stones
Hereditary retinopathy	Retinitis pigmentosa
Huntington's disease	Syndromic craniosynostosis
Hypertrophic obstructive cardiomyopathy	Von Hippel-Lindau
Hypobetalipoproteinemia	

General Device Needs Across Multiple Rare Diseases

Survey respondents were asked to enter up to three general device needs for rare diseases and then answer questions about each need, including the rare disease(s) affected by the need. A complete listing of the 443 cited needs appears in Appendix D.

> *"Advancements in radio-labeled antibodies to pinpoint disease [would detect] malignancies which may be targeted."*
>
> *— Radiologist*

> *"Drug delivery devices that are controlled by feedback from physiologic sensors—Virtually every rare disease where a drug/dose relationship to the severity of disease is known."*
>
> *— Orthopaedic surgeon*

- In describing the needs, 41 percent of the needs were for diagnostic devices, 37 percent were for therapeutic devices, and 21 percent were needs for both diagnostic and therapeutic devices.
- Respondents identified general device needs that may apply to the pediatric population only (24 percent), the adult population only (8 percent), or both (67 percent).
- Respondents indicated that most general device needs pertain to use in either a hospital or clinic setting (78 percent and 73 percent, respectively), although 37 percent identified needs related to use in the home. In addition, 65 percent indicated needs in two or more settings.

Respondents were asked to list the rare disease(s) that would be affected if the need(s) they described was addressed. Table 3 displays examples of general device needs that would address both diagnostic and therapeutic gaps for patients with rare diseases.

Table 3: Examples of General Device Needs Across Rare Diseases

General Device/Test Needs	Rare Diseases That Would Benefit From Met Need
Biomarkers that more closely mirror disease severity and response to therapy	All rare diseases
Device to culture/detect the abnormal cells of the disease if in circulation	Lymphangioleiomyomatosis (LAM), Birt-Hogg-Dubé syndrome
Device to diagnose or screen with high sensitivity and specificity	Genetic diseases and syndromes, autoimmune disorders, pancreatic and other cancers.
Better measures of glomerular filtration rate (GFR)	Chronic kidney disease, acute kidney injury, oncological conditions that require accurate GFR for drug dose.
More individualized prognosis information	Progressive supranuclear palsy, multisystem atrophy, corticobasal syndrome, Huntington's disease, neurodegeneration with brain iron accumulation, dystonia, spinocerebellar ataxia
Devices for blood pressure and systemic blood flow control	Guillain-Barré, dopamine beta-hydroxylase deficiency
Functional testing of known immunodeficient patients	Combined immunodeficiencies, other severe combined immunodeficiency disorders, metabolic disorders
Metabolomics for disease subgrouping	Sarcoidosis, idiopathic pulmonary fibrosis, connective tissue diseases
Noninvasive markers for monitoring disease activity	All eosinophilic gastrointestinal diseases
Serum or non-tissue diagnosis of mitochondrial disease in children	Spectrum of mitochondrial disease, which is often not diagnosed until late, and based on tissue specimen
Tests that allow home monitoring by patients of disease and treatment side effects	Many rare diseases

D. Device Needs for Specified Rare Diseases

This section reviews the survey findings on current unmet device needs for specified rare diseases, as well as current diagnostic and therapeutic device practices for these diseases and respondents' satisfaction with these practices. The data come primarily from a section of the survey that asked respondents to enter up to three rare diseases for which they believe there are device needs and to answer a series of follow-up questions about each disease listed. Because respondents were able to enter between one and three disease-related needs, data were analyzed at the need level rather than the respondent level. Results are reported for the number and types of diseases entered; the diagnostic versus therapeutic device needs for those diseases; the intended population (pediatric and/or adult) and setting of use for those device needs; and current diagnostic versus therapeutic device uses, limitations, and needs.

Discrete Rare Diseases With Unmet Device Needs

A total of 461 discrete rare diseases and conditions were mentioned as having an unmet diagnostic and/or therapeutic device need.[21] Most diseases (69 percent) were mentioned once (see Table 4).

Table 4: Frequency of Mentions for Rare Diseases

Times Mentioned	Number of Diseases	Percentage
Once	321	69%
2–4 times	103	24%
5–9 times	25	5%
10+ times	12	3%

The 10 most cited rare diseases appear in Table 5, with pancreatic cancer and lymphangioleiomyomatosis leading the list. Note that the ranking does not necessarily reflect the urgency of need or prevalence of these diseases, but rather the frequency that they were cited by this survey group, which could be influenced by their involvement with these particular rare diseases.

Table 5: 10 Most Cited Rare Diseases

Disease Name	Frequency of Mentions
Pancreatic cancer	25
Lymphangioleiomyomatosis (LAM)	23
Cystic fibrosis	18
Eosinophilic esophagitis	17
Eosinophilic gastritis	15
Sickle cell disease	15
Pulmonary alveolar proteinosis	14
Huntington disease	13
Mitochondrial disease	12
Multiple myeloma	12

Respondents could enter different device needs for the same disease and, to accommodate this, data were analyzed at the need level rather than the disease level. Table 6 presents the 917 disease-specific diagnostic and therapeutic needs mentioned by the respondents, grouped by medical categories. Respondents mentioned a total of 1,360 device needs for rare diseases when the 917 disease-specified needs were added to the number of general device needs (443) cited by respondents. Complete lists of disease-specific needs cited by the respondents are in Appendix E (Diagnostic Device Suggestions for Specified Rare Diseases) and Appendix F (Therapeutic Device Suggestions for Specified Rare Diseases).

[21] Some of the diseases that respondents cited are considered to be rare only when a subset of the disease or condition that could be treated or diagnosed by a particular device is considered. For example, a non-rare disease may not be considered rare, but in the context of a device, the feature(s) of the device may limit the usage to only the subset of the disease or condition. When responses indicated the need applied to those specific subsets, the disease was included in the results.

Table 6: Categories of Disease-Specific Needs Mentioned*

	Total Needs (N = 917)		Diagnostic Needs (N = 663)	Therapeutic Needs (N = 731)
Medical Category	**Frequency (#)**	**Percentage (%)**	**Percentage (%)**	**Percentage (%)**
Cardiology/Thoracic Surgery/Vascular Surgery/Pulmonary	198	22%	21%	23%
Neurology/Neurosurgery/Psychiatry/Sleep Medicine	197	22%	20%	22%
Hematology/Oncology	132	14%	16%	14%
Metabolism/Endocrinology	118	13%	13%	12%
Gastroenterology/General Surgery	62	7%	8%	7%
Ophthalmology/Otolaryngology	61	7%	5%	7%
Nephrology/Urology	37	4%	5%	4%
Allergy and Immunology/Rheumatology	25	3%	3%	2%
Medical Genetics/Pathology	25	3%	3%	3%
Orthopedics/Plastic Surgery	22	3%	2%	3%
Dermatology	20	2%	2%	3%
Infectious Disease/Toxicology	12	1%	2%	0.3%
General Medicine	4	0.4%	0.3%	0.5%
Obstetrics/Gynecology	3	0.3%	0.5%	0.4%

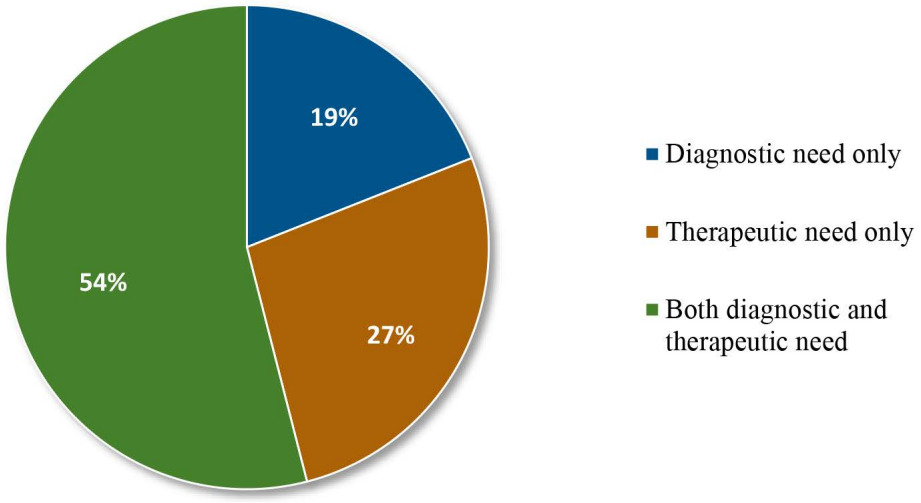
*Some needs were listed as both diagnostic and therapeutic; thus, the percentages for diagnostic and therapeutic needs may not equate to the percentage of all needs within a given medical category.

These data illustrate that diagnostic and therapeutic device needs exist across many medical categories.

Diagnostic, Therapeutic, and Population Needs

Survey respondents were asked about the extent of device needs for diagnosis, therapy, or both, for up to three specific rare diseases. A majority (54 percent) of the diseases cited were reported to have both a diagnostic and therapeutic device need (see Figure 6).

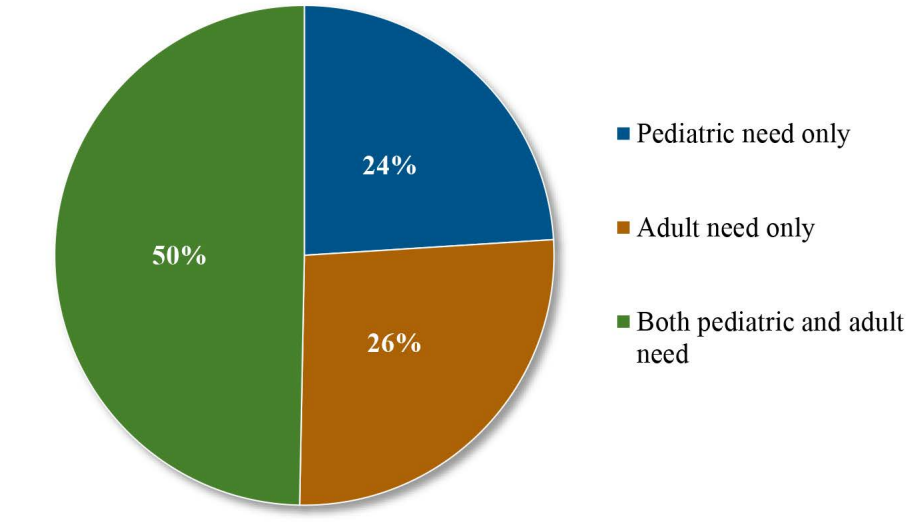
Figure 6: Need Type for Specified Rare Diseases*



*For 14 of the 917 disease-specific needs identified, the respondent did not indicate if the need was diagnostic, therapeutic, or both. These are not included in the figure.

When asked whether the device needs for specified diseases were in either the adult or pediatric population or both, half of the respondents cited needs in both groups, 24 percent cited needs in pediatrics only, and 26 percent cited needs in adults only (see Figure 7).

Figure 7: Population Need for Specified Rare Diseases



Diagnostic Device Needs for Patients With Specified Rare Diseases

For patients with specified rare diseases, respondents believed that creating an entirely new device is most needed, rather than modifying existing devices or repurposing devices for other indications. The limitations of existing diagnostic devices included their lack of sensitivity and specificity and their cumbersome and invasive nature.

Categories of Specified Rare Diseases for Which Diagnostic Device Needs Exist

Table 7 shows the categories of specified rare diseases for which respondents indicated a diagnostic device need. Of those diseases, 266 were mentioned by respondents with a pediatric focus. Appendix E provides a full list of the 663 diseases mentioned as having a diagnostic device need. Responses demonstrated that diagnostic device needs exist across a wide range of rare diseases.

Table 7: Categories of Specified Rare Diseases With Unmet Diagnostic Device Needs

	Needs Mentioned by All Respondents (N = 663)		Needs Mentioned by Pediatric-Focused Respondents (N = 267)	
Disease Categories	**Frequency (#)**	**Percentage (%)**	**Frequency (#)**	**Percentage (%)**
Cardiology/Thoracic Surgery/Vascular Surgery/Pulmonary	136	21%	46	17%
Neurology/Neurosurgery/Psychiatry/ Sleep Medicine	131	20%	54	20%
Hematology/Oncology	108	16%	28	10%
Metabolism/Endocrinology	89	13%	54	20%
Gastroenterology/General Surgery	50	8%	21	8%
Ophthalmology/Otolaryngology	36	5%	12	4%
Nephrology/Urology	30	5%	19	7%
Allergy and Immunology/Rheumatology	22	3%	11	4%
Medical Genetics/Pathology	17	3%	5	2%
Orthopedics/Plastic Surgery	14	2%	9	3%
Dermatology	13	2%	3	1%
Infectious Disease/Toxicology	12	2%	2	0.7%
Obstetrics/Gynecology	3	0.5%	2	0.7%
General Medicine	2	0.3%	1	0.4%

Note: Several needs were grouped into more than one category. See the Methods section and Appendix B for further explanation.

Types of Unmet Diagnostic Device Needs

Of the 467 diagnostic device needs for which respondents completed the question about optimal strategies for meeting the needs, a majority of respondents (70 percent) noted a need for an entirely new device, compared to 20 percent who believed an existing device could be modified. Ten percent stated an existing diagnostic device for a different indication could be repurposed (see Table 8).

Table 8: Options to Meet Diagnostic Device Needs

	Needs Mentioned by All Respondents (N = 467)		Needs Mentioned by Pediatric-Focused Respondents (N = 209)	
Options to Address	**Frequency (#)**	**Percentage (%)**	**Frequency (#)**	**Percentage (%)**
Creation of a new diagnostic device	328	70%	132	63%
Modification (i.e., physical adaptation) of an existing diagnostic device	92	20%	53	25%
Using an existing diagnostic device for a different indication (i.e., repurposing)	47	10%	24	11%

Respondents were also asked to estimate the impact that a new, modified, or repurposed device would have on diagnosing the rare disease. Respondents were nearly evenly divided on whether meeting the need would represent a "breakthrough advancement" (47 percent) or an "important incremental improvement" (46 percent).

When asked in what ways meeting unmet device needs would improve diagnosis from among a list of choices (with the option to select more than one response), respondents chose increased speed (75 percent), improved specificity (70 percent), and improved sensitivity (64 percent). Roughly half (53 percent) said meeting these needs would make diagnosis of rare diseases less cumbersome—for example, by finding a way to avoid the need for extensive and repeated imaging. Forty-four percent indicated that meeting the needs would result in less invasive diagnostics.

Overview of Suggested Approaches for Diagnostic Devices

Respondents were further asked to provide detailed suggestions for how these diagnostic device needs could be met. In total, 419 suggestions were offered. Table 9 summarizes the most common types of devices suggested—many of which would benefit a number of rare disease populations—and details about the need, when indicated. A list of all of the diagnostic device suggestions can be found in Appendix E.

EXAMPLES OF SUGGESTED DIAGNOSTIC DEVICES

"Functional MRI testing to assess primarily neurological versus psychiatric diseases."

"Imaging tests for rare cardiac anomalies such as unicuspid unicommissural aortic valve stenosis."

Table 9: Types of Needed Diagnostic Devices

Biomarker assays
Biopsies–with immunofluorescence, smaller needle
Dynamic MRI
Echocardiography–high resolution
Flow cytometry methods–improved
Functional tests (e.g., cognitive assessments)
Genetic tests–more mutations, more sensitive, more specific, faster, panels, cheaper
Imaging–enhanced, modified for children, improved functional scans
Infrared indirect ophthalmoscope
Improved diagnostic yield from small fluid volumes
Laser Doppler–more available
Metabolomic tests
Molecular-based assays
Non-invasive measures of ventricular refractory period and intraventricular conduction time
Non-invasive intracranial pressure monitor
Predictive tests–prognosis (e.g., biomarkers)
Proteomic tests
Synovial fluid test
Ultrasound–more sensitive

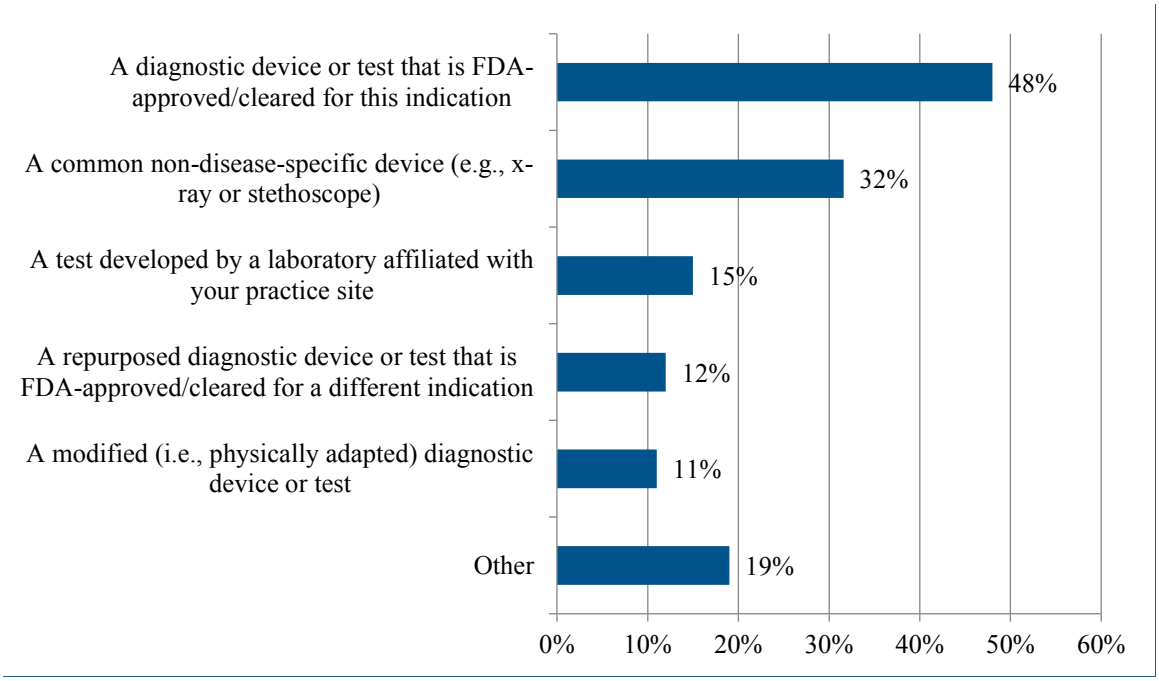
Diagnostic Device Needs in Various Settings

Finally, respondents suggested diagnostic devices could be used in multiple settings. For example, 84 percent of the suggested diagnostic device needs could be used in the clinic setting, 76 percent could be used in the hospital setting, and 44 percent could be used in the home. In total, 73 percent of the suggested diagnostic devices could be used in two or more settings.

Uses and Limits of Current Diagnostic Devices

Respondents currently use a device to diagnose 329, or 76 percent, of the diseases cited. Figure 8 shows the types of devices used.

Figure 8: Types of Devices Currently Used for Diagnosing Rare Diseases*



*Some respondents indicated they use more than one type of device to address the diagnostic need; thus, the percentages sum to more than 100 percent.

Respondents with a pediatric focus were slightly more likely to use a diagnostic device developed by a laboratory affiliated with their practice site (23 percent versus 15 percent).

If respondents indicated that they were not using such a diagnostic device, they were asked to indicate what other approaches they use to diagnose the disease, using a list of several options. For the 105 responses fitting this category, most (73 percent) noted they rely on symptoms and/or medical history to make a diagnosis, and 56 percent stated they rely on physical exams (see Table 10). Among the "other" responses were biopsies, general "labs," genetic tests, and imaging. Although some of the choices in this category are what the FDA considers medical devices, they are likely so commonly used in the clinical setting that respondents consider them to be "tools" rather than diagnostic devices.

Table 10: Other Approaches Currently Used for Diagnosing Rare Diseases*

Diagnostic Approach	Frequency	Percent
Symptoms and/or medical history	77	73%
Physical exams	59	56%
Genetic tests	48	46%
General labs	39	37%
Imaging	39	37%
Pathology/biopsy tests	39	37%
Functional/performance tests	18	17%
Other methods	11	10%

*Some respondents indicated they use more than one diagnostic approach to address the diagnostic need; thus, the percentages sum to more than 100 percent. Further, although some of the choices in the survey are considered medical devices by the FDA, these devices are so commonly used that there was concern that these choices were considered tools and not diagnostic devices. Therefore, these devices were given as choices to fully capture the method(s) that the respondent used to diagnose the disease.

Most of these respondents (81 percent) reported using a combination of two or more of these approaches. Notably, genetic tests, which are regulated as devices, are critical tools for the diagnosis (and appropriate treatment) of many rare conditions, and the serious shortage of them was mentioned repeatedly by survey respondents in open-ended questions.

> *"The biggest challenge is the cost of doing detailed genetic testing in infants with rare diseases like polycystic kidney disease, central apnea, inborn errors of metabolism, etc."*
>
> *— Pediatrician*

Finally, respondents were asked to describe any limitations of existing diagnostic devices. The results, with examples, appear in Table 11. (The full list of 301 limitations is provided in Appendix G.)

> *With regard to amyotrophic lateral sclerosis (ALS), "There is no way to diagnose until later onset. Novel blood test, imaging, or other nerve tests needed ... A non-invasive [test], such as blood test, to diagnose ALS in its early stage."*
>
> *— Pathologist*

Table 11: Limitations of Currently Available Diagnostic Devices for Rare Diseases

Limitation to Diagnostic Devices or Tests	Percentage	Example
Invasive, cumbersome, painful and/or inconvenient	25%	"Kidney biopsy is invasive."
Lack specificity	20%	"MRI and PET not specific for sarcoid."
Costly or often not covered by insurance	14%	"Upper endoscopy—expensive and inconvenient."
Unreliable, inaccurate, or subjective	15%	"The current available serological tests are somewhat nonspecific and not confirmatory of the condition."
Lack sensitivity	10%	"The tumors are not readily seen until they are ~2 cm in diameter, at which point most are already metastasized."
Lack granularity to distinguish subtypes, prognosis, or response to therapy	7%	"Current serologic tests do not distinguish between filarial diseases."
Take too long	13%	"Currently, available testing can take many weeks…"
No single, comprehensive device or test is available	7%	"We piece together a diagnosis from clinical, radiologic, and occasional genetic information. It is a best guess."
Do not provide early detection, diagnosis, or screening	8%	"Need a test that diagnoses pancreatic cancer sooner so that it can be treated sooner."
Lack of availability	7%	"Conditions cannot be diagnosed until clinically evident. There is currently no newborn screen."
Other	16%	"Not validated," "No direct assay," Nothing available," "Have to rely on multiple tests," "Suboptimal"

Therapeutic Device Needs for Patients With Specified Rare Diseases

Across all types of rare diseases, respondents reported that meeting therapeutic device needs would improve the quality of life and survival rate for patients with rare diseases. Nearly six out of 10 respondents were dissatisfied with the options they had, and 67 percent believed that entirely new therapeutic devices are needed. Respondents cited complications, side effects, unacceptable outcomes, and lack of options as limits they face with existing devices in caring for this population.

Categories of Specified Rare Disease for Which Therapeutic Device Needs Exist

Therapeutic device needs exist across a wide range of rare diseases. Table 12 shows the categories of specified rare diseases for which a total of 731 therapeutic device needs were mentioned. Of those needs, 277 were mentioned by clinicians with a pediatric focus. (See Appendix F for a full list of the diseases mentioned as having a therapeutic need.)

Table 12: Categories of Specified Rare Diseases With Unmet Therapeutic Device Needs

	Needs Mentioned by All Respondents (N = 731)		Needs Mentioned by Pediatric-Focused Respondents (N = 277)	
Disease Category	**Frequency (#)**	**Percentage (%)**	**Frequency (#)**	**Percentage (%)**
Cardiology/Thoracic Surgery/Vascular Surgery/Pulmonary	165	23%	65	23%
Neurology/Neurosurgery/Psychiatry/Sleep Medicine	162	22%	57	21%
Hematology/Oncology	99	14%	21	8%
Metabolism/Endocrinology	88	12%	47	17%
Ophthalmology/Otolaryngology	53	7%	16	6%
Gastroenterology/General Surgery	49	7%	18	6%
Nephrology/Urology	31	4%	16	6%
Medical Genetics/Pathology	21	3%	7	3%
Orthopedics/Plastic Surgery	21	3%	13	4%
Dermatology	18	2%	6	2%
Allergy and Immunology/Rheumatology	15	2%	6	2%
General Medicine	4	0.5%	3	1%
Obstetrics/Gynecology	3	0.4%	2	0.7%
Infectious Disease/Toxicology	2	0.3%	0	0.0%

Types of Unmet Therapeutic Device Needs

When asked how to best fulfill the therapeutic device needs for the specified diseases mentioned, a majority (67 percent) of respondents cited the need for an entirely new device, 19 percent responded that an existing device could be modified, and 14 percent stated an existing therapeutic device for a different indication could be repurposed. Similar percentages were recorded for those with a pediatric focus (see Table 13).

Table 13: Options to Meet Therapeutic Device Needs

	Needs Mentioned by All Respondents (N = 474)		Needs Mentioned by Pediatric-Focused Respondents (N = 208)	
Options to Address	**Frequency (#)**	**Percentage (%)**	**Frequency (#)**	**Percentage (%)**
Creation of a new therapeutic device	316	67%	134	64%
Modification (i.e., physical adaptation) of an existing therapeutic device	91	19%	43	21%
Using an existing therapeutic device for a different indication (i.e., repurposing)	67	14%	31	15%

Respondents were also asked to estimate the impact that a new, modified, or repurposed device would have on treating the rare disease. Over half of respondents believed that meeting the need would represent a "breakthrough advancement" (57 percent), while 38 percent indicated the device would represent an "important incremental improvement."

When asked in what ways meeting unmet device needs would improve treatment of the rare disease, respondents chose the following from a list of options, with the option to select more than one response:

- Improved quality of life (86 percent)
- Prolonged survival (62 percent)
- Restored or replaced organ function (54 percent)
- Temporary relief (35 percent)
- Other (10 percent)

Again, responses among those who indicated a pediatric specialty were similar.

Overview of Suggested Approaches for Therapeutic Devices

When asked for descriptions of details of these therapeutic device needs, approximately 400 suggestions were offered. Table 14 summarizes the most common types of devices suggested—many of which would benefit a number of rare disease populations—and details about the need, when indicated. All of the responses can be found in Appendix F.

Table 14: Types of Needed Therapeutic Devices

Artificial heart
Artificial lung
Balloon angioplasty device–smaller diameter and tip, anchored, detachable
Biomaterials–biocompatible, bioresorptive capacity, 3-D printing
Bridges for occlusions
Catheters–smaller, absorbable, pediatric specific, autologous
Cell separation devices
Corneal crosslinking and lenses
Closure devices–biodegradable
Deep brain stimulation with imaging and electrophysiological targeting
Defibrillators–implantable
Dialysis devices–smaller, for neonates
Electroporation or energy device
Epidermal and dermal replacement
Filter devices–smaller
High resolution echocardiography
Imaging–more specific
Implants–orthopedic, prolonged drug delivery, cell preservation
Implantable cardioverter defibrillator–smaller
Joint implants–smaller
Lengthening device for spine
Monitoring devices for use at home
Muscle or nerve stimulator
Negative pressure wound dressing and chelating agents
Neuroprothesis–hearing; vision; movement
Ocular surface replacement
Pumps to administer treatment
Radioactive bone cement

Radiofrequency ablation devices
Rechargeable technology
Scaffolds–biodegradable
Soft tissue grafts
Stents–supra choroidal, biodegradable, absorbable, adhesive
UV light delivery systems
Valve replacements, valve repair
Ventricular assisted devices–adaptable, smaller
Vertical expandable rib

EXAMPLES OF SUGGESTED THERAPEUTIC DEVICES

For transverse vaginal septum:

"Adolescents who have surgery for vaginal transverse septa are at risk for vaginal stenosis. Current stents are cumbersome and difficult for these girls to use. An appropriately sized and configured vaginal stent is needed to prevent restenosis after surgery to remove transverse vaginal septa. Bioengineering needed to develop the materials and the correct configuration—the vagina is (not) a cylinder, and thus current dilators and stents do not fit the vagina well."

For pancreatic cancer:

"We need a device to help treat patients with locally invasive and/or disseminated disease (Stages 3 and 4). One idea is the use of electroporation or some sort of energy device that would selectively damage locally invasive cancers without injury to surrounding/adjacent tissues."

For fatal diseases in infancy with mutated protein product:

"Implantable device that would allow cells to survive that would produce the missing normal protein continuously over long periods of time."

Therapeutic Device Needs in Various Settings

The suggested therapeutic devices often can be used in a number of different settings. For example, 76 percent of these therapeutic devices can be used in the hospital; 76 percent can be used in the clinic setting; and 51 percent can be used in the home. Of note, 72 percent of these therapeutic devices can be used in two or more settings.

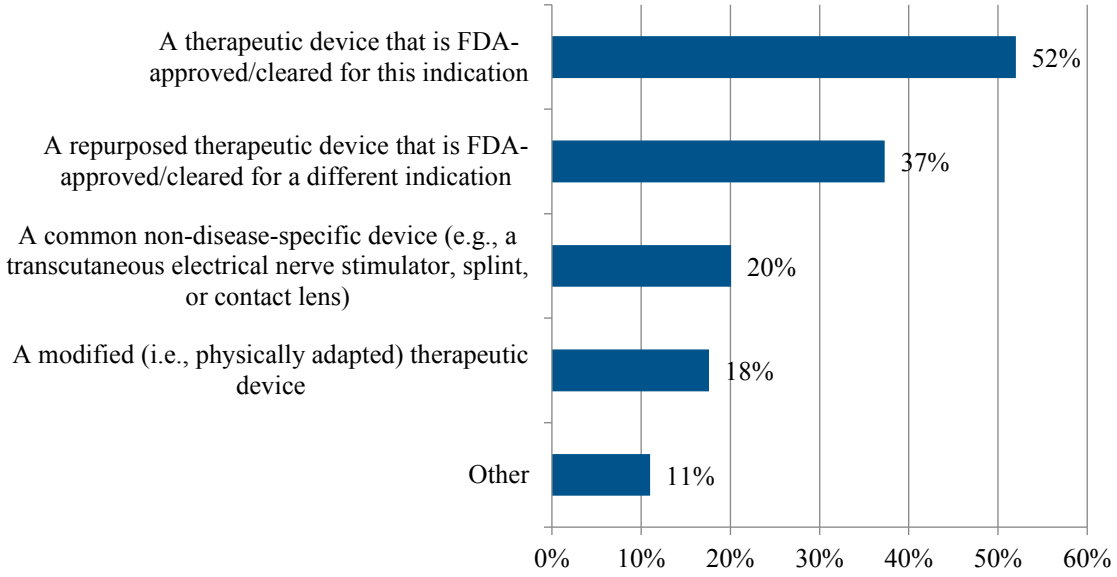
Uses and Limits of Current Therapeutic Devices

Of the 431 therapeutic needs for which respondents reported whether they use any medical devices for treatment, respondents indicated they use a therapeutic device for 245 (57 percent) of them. Of the 245, 52 percent were treated with a device that was FDA-approved or cleared for such an indication. As shown in Figure 9, roughly 55 percent of respondents either repurposed a device that was approved or cleared for a different purpose or used a modified device.

"The current devices available to close preemie PDAs [patent ductus arteriosus] are not designed for or approved for this indication."

— Clinical specialty unknown

Figure 9: Types of Devices Currently Used for Treating Rare Diseases*



*Some respondents indicated they use more than one type of device to address the therapeutic need; thus, the percentages sum to more than 100 percent.

For those diseases for which clinicians reported not using devices for treatment, 11 percent do not have an existing treatment. Of those diseases that do have a current non-device treatment option, drugs were the most commonly reported therapeutic approach (78 percent), followed by use of a biological product (22 percent), medical food (14 percent), or a genetic product (4 percent).

Clinicians delineated several limitations to the current therapeutic devices. The full list of 225 responses is provided in Appendix H. Table 15 displays the most commonly mentioned limitations.

Table 15: Limitations to Current Therapeutic Devices

Limitation to Therapeutic Devices	Percentage	Example
Risks of complications/ possible side effects	20%	"Multiple devices, such as detachable coils must be used to close the CCF [carotid cavernous fistula] from within the cavernous sinus. The parent vessel may ultimately have to be sacrificed. Often the ICA [internal carotid artery] caliber will be too large to accommodate a flow-diverting stent. Use of other devices adds to treatment complexity and increases risk to the patient."
Poor, variable, or unreliable efficacy/outcomes	17%	"Poor efficacy of amniotic membrane transplant. Poor success of corneal transplant surgery or keratoprosthesis surgery."
Current options are insufficient/other options would be better	24%	"Requires two anti-platelet agents, too many rebleeds and thrombotic complications."
Does not cure/treat the underlying causes or prevent	13%	"Most devices modify the visual input (e.g., magnification, contrast) rather than treat the disease itself."

Limitation to Therapeutic Devices	Percentage	Example
Not approved for pediatrics/limitations in usage for young patients	11%	"All but one valve device are FDA-approved only for adults. They are used off-label in pediatric applications."
Expensive/no insurance coverage	8%	"No 3rd party payment possible, which is a hardship for physicians and, especially, affected families."
Not designed and/or FDA-approved for this application	8%	"Ozurdex implant is not FDA-approved for this indication, therefore not paid by insurance and extremely expensive."

Pediatric Therapeutic Devices

Slight differences in responses from respondents with a pediatric focus were noted for therapeutic device needs, but such differences were not found in responses pertaining to diagnostic devices. Respondents with a pediatric focus were slightly more likely to agree that a modified or repurposed device, or a device approved for another indication—rather than a new device—would best address therapeutic needs (36 percent versus 32 percent; 64 percent versus 68 percent for entirely new devices). Such devices include, for example, stents or catheters fitted to smaller sizes. With regard to current treatment devices used, 55 percent of those with a pediatric focus used an FDA-approved device for this indication and 23 percent used a modified device. In contrast, 50 percent of respondents without a pediatric focus use an FDA-approved device for this indication and 12 percent used a modified device.

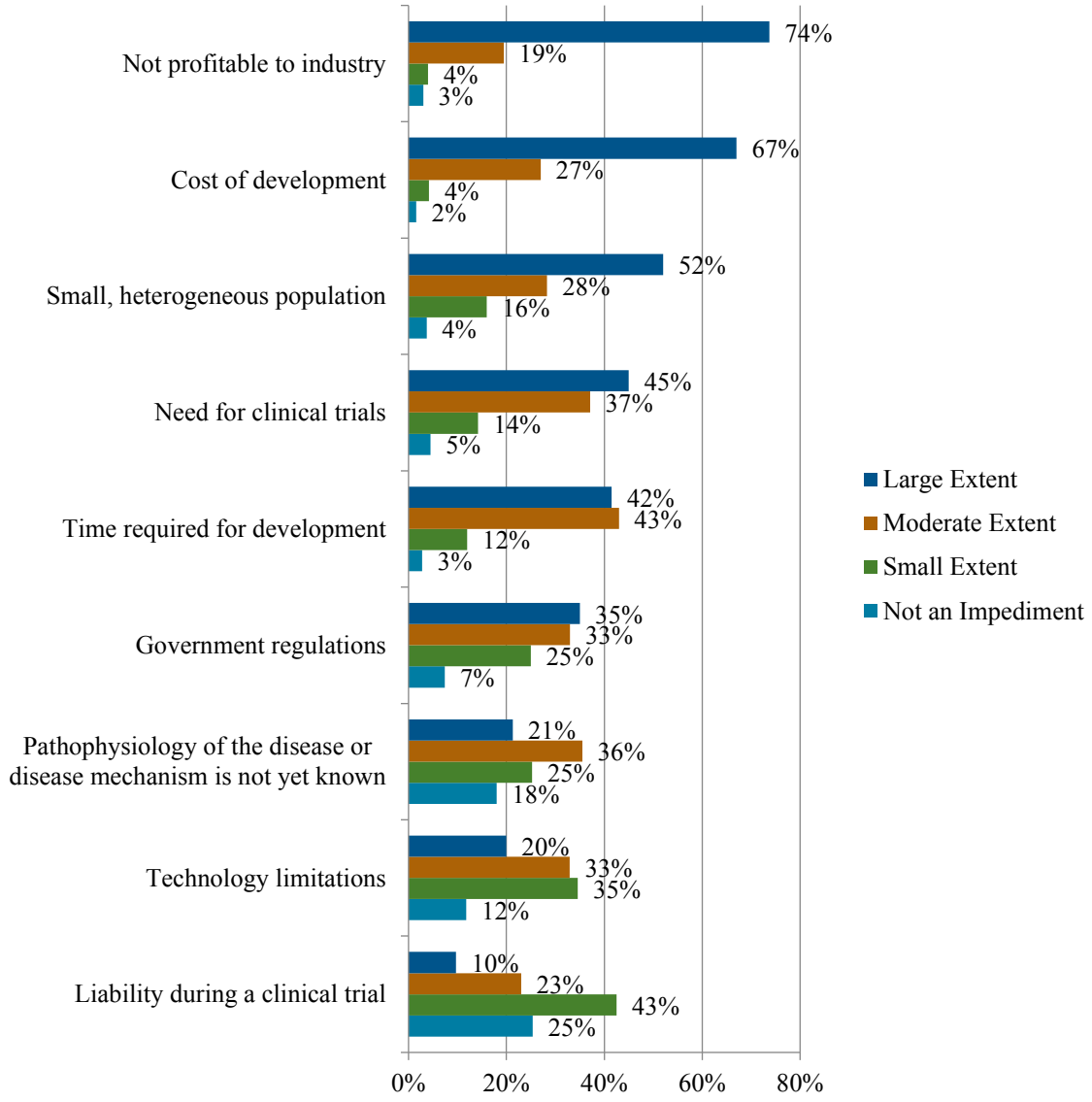
E. Meeting the Needs to Improve Diagnosis and Treatment

Across all types of rare diseases, respondents agreed that meeting device needs would improve the diagnosis and treatment for patients with rare diseases. However, the costs of research and development, lack of profitability for industry, and the challenges of conducting trials in small, heterogeneous populations were obstacles to progress in this area. Notably, genetic tests, which are regulated as devices, are essential tools for the diagnosis of many rare diseases and conditions, and the critical shortage of them was mentioned repeatedly by survey respondents. In addition, half of the respondents were aware of the HUD/HDE regulatory pathway for device development, and 94 percent of these respondents found that the pathway was helpful for device development, though they also noted challenges in using it.

Impediments and Challenges in Device Development

All respondents were asked to indicate the extent to which they believe a series of factors hinder the development of devices for rare diseases, regardless of their past experience with development and testing. Of the 444 respondents who addressed this question, lack of profitability for industry was cited by 74 percent as a leading impediment to device development (see Figure 10). In addition, 67 percent of respondents cited the cost of development as a major obstacle. The time required for development and government regulations was seen as less of a barrier. Respondents also cited scientific and technical challenges in device development for rare diseases, along with the heterogeneous nature of rare diseases (this was the one area where the percentages substantially differed between all respondents and those with a pediatric focus). Of note, few respondents selected liability during a clinical trial as an impediment.

Figure 10: Perceived Impediments to Medical Device Development for Rare Diseases (N = 454)



Note: Results from those with a pediatric focus were similar, with the exception that slightly more (59 percent, compared to 52 percent of all respondents) responded that the small heterogeneous nature of the patient population was to a large extent an impediment.

Respondents whose patient population included at least one patient age 21 or younger were asked to describe any challenges they have in diagnosing or treating pediatric patients with rare diseases. Although the responses varied, a few themes emerged. In brief, respondents most frequently cited insufficient insurance coverage for use of diagnostic and therapeutic devices as an impediment to access to care (35 of 215 responses, or 16 percent). Diagnostic challenges related to sensitivity and specificity or timeliness were each mentioned by 15 percent of those who responded. Among the other challenges listed were a lack of knowledge about pediatric populations, insufficient evidence about diagnostic or treatment options for children with rare diseases, and insufficient access to

appropriate experts or facilities because of geographic location (less than 5 percent of all responses). The list of challenges described is provided in Appendix I.

Humanitarian Use Devices

At the time of the survey, a HUD was defined as a medical device intended to treat or diagnose a disease or condition affecting fewer than 4,000 individuals in the United States per year. However, the population estimate required to qualify for HUD designation changed on Dec. 13, 2016, from "fewer than 4,000" to "not more than 8,000," through Section 3052 of the 21st Century Cures Act (Pub. L. No. 114-255). An HDE is the FDA marketing application that may modify or reduce certain data requirements for HUD developers and has a different statutory requirement for approval, known as safety and probable benefit. Respondents indicated that while the HDE provides a useful pathway to bring devices to market, there are obstacles to its use.

Half of the 461 respondents who responded to a question regarding awareness of the HUD/HDE pathway for device development (51 percent) indicated they were aware of it. Of the 210 respondents who reported on the pathway's helpfulness in developing devices, 25 percent indicated it is very helpful, 33 percent reported it is helpful, and 36 percent stated it is somewhat helpful. Only 6 percent reported the HUD/HDE pathway to be not helpful in meeting the needs of rare disease populations.

When asked whether they had experienced specific challenges in using HUDs, securing reimbursement, gaining access, and contending with IRB constraints were each cited by roughly half of the 177 respondents who addressed this question and by roughly half of the 79 respondents with a pediatric focus who addressed this question (see Table 16). Furthermore, meeting patient eligibility requirements was cited as a barrier by approximately one in three respondents. Fewer respondents cited a less-than-expected benefit to the patient or safety.

Table 16: Challenges in Using Humanitarian Use Devices

	Challenges Reported by All Respondents (N = 177)		Challenges Reported by Pediatric-Focused Respondents (N = 79)	
Challenges	**Frequency (#)**	**Percentage (%)**	**Frequency (#)**	**Percentage (%)**
Reimbursement	92	52%	38	48%
Access to Humanitarian Use Devices	88	50%	36	46%
IRB constraints	81	46%	36	46%
Patient eligibility	64	36%	22	28%
Less than expected benefit to the patient	34	19%	11	14%
Safety	33	19%	14	18%
Other	29	16%	15	19%

Patients with rare diseases face a number of challenges in the clinical setting, from diagnosis to treatment to ongoing care. A fundamental obstacle to drug and device development for these diseases is that often very little is known about their pathophysiology or natural history. And for those with a genetic component, there can be substantial heterogeneity and variability in genotype and phenotype, which confounds both diagnosis and treatment. Further, each of these diseases affects a small number of patients, which not only creates scientific challenges in terms of conducting robust clinical trials but also raises investment and regulatory challenges.

Orphan drug legislation has been successful in spurring rare disease drug development. In 1990, Congress authorized the HUD/HDE program to encourage the development and introduction of needed device technologies for diseases with small patient populations. However, device needs in rare diseases persist even though the 21st Century Cures Act of 2016 increased the HUD designation threshold for devices intended to treat or diagnose a disease or condition that affects or is manifested in no more than 8,000 individuals per year. Fostering innovation and device development for patients with rare diseases who may benefit from medical devices is of great importance to FDA and NCATS/ORDR, which have undertaken a number of initiatives to promote device development and testing.[22]

To further advance medical device development for rare disease patients, FDA and NCATS/ ORDR partnered to conduct this needs assessment to (1) better understand unmet medical device needs for rare diseases across the various medical specialties, (2) generate meaningful data to inform patients, practitioners, policy makers, and device developers on the needs, barriers, and incentives related to medical device development for rare diseases, and (3) increase public awareness of these needs. To address the large proportion of pediatric rare disease patients, the assessment also focused on pediatric medical device needs. There was no intent to prioritize needs by disease or to emphasize needs in one population over any other.

Key Findings

The survey had a high response rate at 44 percent. Results confirm a previously held assumption that the need for rare disease devices is great. The vast majority of respondents (90 percent) believed at least one of the rare diseases with which they were familiar was in need of new or improved medical devices. Moreover, it was confirmed that needs exist across diagnostic and therapeutic devices and across pediatric and adult patient populations.

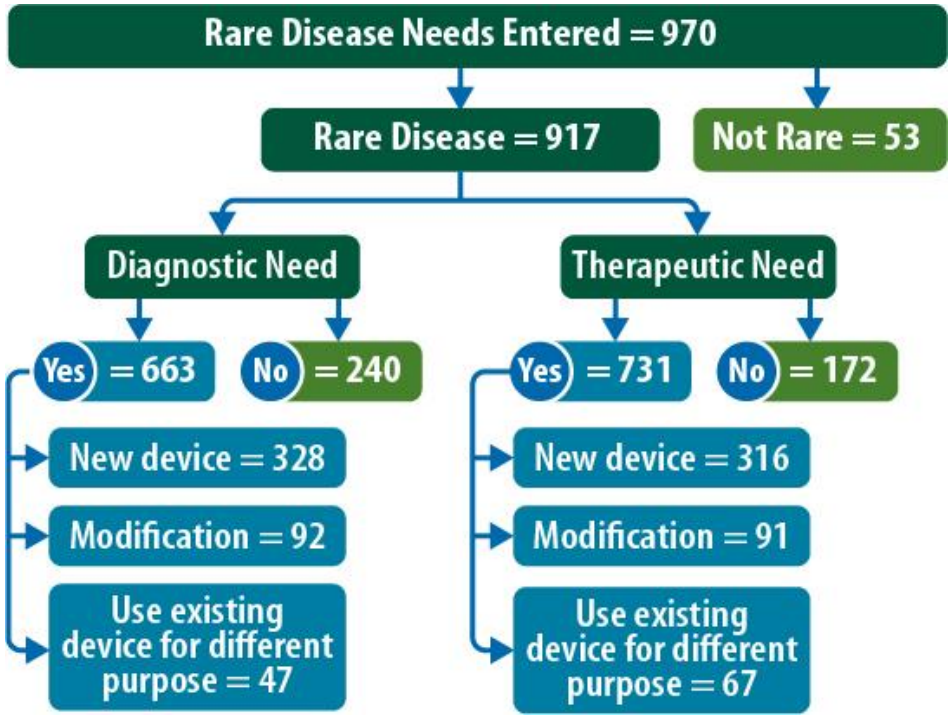
A total of 461 diseases/conditions covering all major medical specialties were suggested to have a diagnostic and/or therapeutic device need, with a majority of diseases/conditions mentioned only once, which highlights the quantity and heterogeneity of needs. It also emphasizes that needs exist across hundreds of rare diseases; that is, they are not concentrated in a small category of conditions, limited to specific organs, or confined to a few medical specialties. Although a broad range of diseases was cited, the range was limited by the expertise and participation of the survey respondents. A further limitation was overrepresentation by clinicians practicing in academic medical centers; however, these are the settings in which patients are more likely to find expertise on rare diseases. Importantly, given the large pediatric population with rare diseases, an overwhelming majority (97 percent) of the respondents with a pediatric focus (i.e., clinicians who selected pediatrics or a pediatric specialty as

[22] Mokhtarzadeh, M, Eydelman, M, Chen, E. Challenges and opportunities when developing devices for rare disease populations. *Expert Opinion on Orphan Drugs*, *4*(5), 457–459. 2016. doi: 10.1517/21678707.2016.1166948

their focus and those who reported that at least half of their patients are 21 years old or younger) reported having direct experience diagnosing or treating patients with rare diseases. Results of the survey provided a substantial level of clinician input on medical device needs for the pediatric population.

Figure 11 outlines some of the most striking findings from the survey about the magnitude of needs, types of needs, and best methods to address those needs. Respondents plainly believe that creating an entirely new device is what is most needed (70 percent for diseases with a diagnostic need and 67 percent for disease with a therapeutic need) rather than modifying existing devices or repurposing devices approved for other indications. This belief underlines the critical need for greater device development and testing. Overall, respondents were more dissatisfied with existing therapeutic devices than with diagnostic devices.

Figure 11: Overall Device Needs for Rare Diseases*



*Respondents were able to select both diagnostic and therapeutic needs. Thus, the N for diagnostic need and the N for therapeutic need sum to greater than the N for all rare disease/disease subtypes. In addition, the N for new device, modification, and use existing device for a different purpose do not sum to the N for yes responses under either the diagnostic or therapeutic need because not all respondents selected a response for the question of how the need identified could best be addressed.

The limitations of existing diagnostic devices included their lack of sensitivity and specificity and their cumbersome and invasive nature. Across all types of rare diseases, respondents agreed that meeting diagnostic device needs would improve care for patients with rare diseases. Across both therapeutic and diagnostic devices, the costs of research and development and lack of profitability for industry, as well as the challenges of conducting trials in small, heterogeneous populations pose barriers to progress in this area. Notably, genetic tests, which are regulated as devices, are essential tools for the diagnosis and treatment of many rare conditions, and their critical shortage was mentioned repeatedly by survey respondents.

With regard to therapeutic devices, respondents agreed that meeting therapeutic device needs would improve quality of life and survival for patients with rare diseases. Nearly six in 10 were dissatisfied with the options they have, and two-thirds believed that entirely new therapeutic devices are needed. Respondents cited complications, side effects, unacceptable outcomes, and lack of options as limits they face in caring for this population with the existing therapeutic devices.

Key Pediatric Findings

The survey also attempted to gain insight into whether there were unique needs for pediatric patients with rare diseases. One-third of respondents had pediatric experience. Respondents cited device needs specific to pediatric populations (24 percent) as well as needs applicable to both pediatric and adult populations (50 percent), indicating that 74 percent of device needs pertain to the pediatric population. Other than the expected needs related to the size of devices or their invasiveness—which is more concerning with children—needs in this pediatric population generally match those in the overall population. Table 17 provides some examples of device needs specific to the pediatric population. In addition, respondents tended to list the same challenges and impediments for both diagnostic and therapeutic devices.

Table 17. Examples of General Device Needs for Pediatric Rare Disease Patients

General Device/Test Needs
Better endoscopic devises for hepatic and pancreatic screening in children
Better imaging techniques for little patients, pediatric age
Devices that grow with a child … cardiac valve conduits that could expand with a growing child so that they are not requiring repeated surgeries during their lifetime
Devices to improve ambulation or prevent falls for children with refractory movement disorders
Growing joint prosthesis for children
Implantable chemotherapy delivery devices for children
Intrathecal catheters for pediatric patients that accommodate growth
Pediatric devices for fracture fixation
Pediatric-sized cardiovascular devices

As discussed in this report, respondents whose patient population includes at least one patient 21 years or younger were asked to describe any challenges they had faced in diagnosing or treating pediatric patients with rare diseases. The more common challenges were insufficient insurance coverage for use of diagnostic and therapeutic devices as an impediment to access to care (16 percent) and diagnostic challenges related to sensitivity and specificity or timeliness (15 percent).

Clinicians with a pediatric focus were slightly more likely than overall respondents to report modifying or repurposing a therapeutic device, as well as being slightly more likely to treat off-label with a device. This is potentially due to a lack of adequate devices; that is, long-term paucity of needed devices forced clinicians to innovate on their own by adapting available devices for pediatric use. Even though the results across adult and pediatric populations were relatively similar, it is clear that there are greater challenges facing device development for children with rare diseases. Responses to open-ended questions suggest that one type of modification or

repurposing of devices relates to resizing the device for pediatric use. This group of respondents cited the same benefits of meeting needs as the general population—that is, improved quality of life and survival. Clinicians with a pediatric focus also were slightly less likely to call for entirely new diagnostic devices than the overall respondents. Even so, 63 percent cited the need for entirely new devices. These clinicians were slightly more likely to use a diagnostic device that had been developed by a laboratory affiliated with their practice institution. Responses to open-ended questions cited reliance on assays or molecular tests available through their institutions' clinical and research laboratories.

In response to questions about specific device needs in the pediatric population, 65 percent of respondents with a pediatric focus reported that pediatric implants that grow with a child are an unmet need, and 44 percent reported pediatric intrathecal ports for drug delivery as an unmet need.

Conclusions and the Way Forward

The goal of this needs assessment was to document the shortfalls in medical devices for rare disease patients and to gain a better understanding from stakeholders experienced with rare diseases of the adequacy of the currently available devices. The results demonstrate that more and improved devices are needed to help shorten the diagnostic odyssey, provide treatment options, and improve the quality of life for individuals living with a rare disease. The needs assessment also verifies a previously held assumption that unmet medical device needs continue to mitigate optimal care for children and adults with rare diseases.

It is essential to view these results from the perspective of rare disease patients and the clinicians who care for them. For many, no devices are available for diagnosis or treatment. For others, the options for existing devices are limited or suboptimal. Because medical device needs for rare diseases may be highly specific, device developers face multiple challenges, particularly with economies of scale. The enhanced awareness of device needs provided through this needs assessment, along with improved clarity regarding specific needs, offers the groundwork for developing solutions. The incentives to produce small numbers of vastly specialized devices need to be considered, given the relatively high development and production costs. Furthermore, although survey respondents clearly expressed a desire for entirely new devices (which could reflect a total absence of devices to treat a particular disease), it is worth reviewing existing devices to determine whether they can be usefully modified or repurposed for the rare disease populations, which might be completed at a lower cost and with more favorable economies of scale.

To address these issues, FDA and NIH provide programs to encourage the development of devices that address unmet medical device needs and programs that offer funding incentives to assist with a product's clinical development. These programs are described below to help the rare disease community build an effective ecosystem for developing rare disease devices:

- **A 2014 FDA strategic plan on pediatric rare diseases** included sections on specific medical device strategies (part of a full report at http://bit.ly/1r6IBCF).
- **The FDA/CDRH Expedited Access Pathway Program**, for certain medical devices, is intended to reduce the time and cost from development to marketing decisions without changing the regulatory standards for approval or standards of valid scientific evidence (http://bit.ly/2kaEL0R).
- **FDA/CDRH Early Feasibility Studies** is a program for early clinical evaluation of devices to provide proof of principle and initial clinical safety data (http://bit.ly/2jHk8st).

- **FDA/CDRH Extrapolation to Pediatric Uses of Medical Devices** is a program that allows leveraging relevant clinical data, when appropriate, to support devices being granted marketing approval for pediatric indications (http://bit.ly/2jGOZVM).
- **FDA/OOPD Clinical Trials Grants Program** provides grant funding for rare disease clinical studies on safety and/or effectiveness data for market approval of products for use in rare diseases or conditions (http://bit.ly/2jGVxDR).
- **FDA/OOPD Pediatric Device Consortia Grant Program** funds nonprofit consortia to facilitate the development, production, and distribution of pediatric medical devices (http://bit.ly/O1TY05).
- **NCATS/ORDR at NIH offers NCATS small-business funding** designed specifically to transform the translational science process so that new treatments and cures for disease can be delivered to patients more quickly. NCATS supports the development of clinical technology, instruments, devices, and related methodologies that may have broad application to clinical research and better patient care. NCATS' Small Business Innovation Research and Small Business Technology Transfer (SBIR/STTR) areas of interest can be found at https://ncats.nih.gov/smallbusiness/resources.
- **Other SBIR/STTR programs and initiatives at NIH** support device development, such as the programs that support device development by the NIH National Institute of Biomedical Imaging and Bioengineering (NIBIB).
- **Several programs within the NIH NIBIB Division of Discovery Science & Technology** may be of interest for medical device development. (https://www.nibib.nih.gov/research-funding). Here are brief descriptions of these programs:
    - *Biomaterials*: supports the research and development of new or novel biomaterials that can be used for a broad spectrum of biomedical applications such as implantable devices, tissue engineering, imaging agents, and biosensors and actuators.
    - *Delivery Systems and Devices for Drugs and Biologics*: Includes the delivery of nucleic acids, peptides, proteins, vaccines, genes, small molecules, and theranostics. Emphasis is on the engineering of new delivery vehicles that may include (but are not limited to) novel biomaterials, liposomes, micelles, nanoparticles, and dendrimers; or various delivery modalities that may include, for example, ultrasound, electroporation, implantable pumps, or stimulators.
    - *Integration of Implantable Medical Devices*: Supports the design, development, evaluation, and validation of medical devices and implants, vis-à-vis their interface to the host.
    - *Micro- and Nano- Systems; Platform Technologies*: Supports the development of BioMEMS, microfluidics, and nanoscale technologies, including micro-total analysis systems, arrays, and biochips, for detection and quantitation of clinically relevant analytes in complex matrices. Application areas include biomedical research, clinical laboratory diagnostics, high-throughput screening, and implantable devices, among others.
        - *Rehabilitation Engineering:* Supports next generation engineering technology for rehabilitation engineering research. Application areas include early stage

technology development of neuroprosthesis and neuroengineering systems, Brain Computer Interface (BCI) technology, robotics for rehabilitation, bio-mechanics of human movement. Specific technologies include the development of intelligent hardware and software for the control of devices and the prediction of physiological signals and human behavior.

- *Rehabilitation Engineering, Clinical, Assistive, and Implantable Medical Devices (RECLAIMED)*: Supports next generation, engineering technology for implantable and assistive medical devices. Technologies for implantable medical devices include early stage technology development for implantable neuroprosthesis and neuroengineering systems, and next generation neural interfaces. Technologies for assistive medical devices include medical robotics for rehabilitation, surgery, preventive health and therapy; and next generation prosthetics and BCI technology.
- *Biosensors:* Covers the development of sensor technologies for the detection and quantitation of clinically relevant analytes in complex matrices. Application areas include (among others) biomedical research, and clinical laboratory diagnostics, covering in vitro diagnostics, noninvasive monitoring, and implantable devices. Technologies encompassed include novel signal transduction approaches, materials for molecular recognition, biocompatibility, signal processing, fabrication technologies, actuators, and power sources.
- *Surgical Tools, Techniques and Systems:* Supports the research and development of next generation tools, technologies, and systems to improve the outcomes of surgical interventions. Examples include medical simulators for surgical training and increased patient safety, surgical robotics, and devices for minimally invasive surgeries.

- **NIBIB SBIR/STTR program.** The NIBIB welcomes SBIR and STTR applications from small businesses proposing research and development in various areas of biomedical imaging and bioengineering (access through https://www.nibib.nih.gov/research-funding/small-business-innovation-research-and-small-business-technology-transfer-program-0).

  Biomedical imaging research supported by the NIBIB includes imaging device development, biomedical imaging technology development, imaging processing, imaging agent and molecular probe development, informatics and computer sciences related to imaging, molecular and cellular imaging, bioelectrics/biomagnetics, organ and whole body imaging, screening for diseases and disorders, and imaging technology assessment.

  Bioengineering research support by the NIBIB includes biomaterials, biomechanics and rehabilitation engineering, tissue engineering, medical devices and implant science, therapeutic agent delivery systems, biosensors, platform technologies, nanotechnology, mathematical models and computation algorithms, bioinformatics and medical informatics, remote diagnosis and therapy, image- guided interventions, and surgical tools and techniques.

These government programs that are already in place may facilitate device development for rare diseases. In addition, this report shows the need for rare disease stakeholders and policy makers to further incentives and programs to accelerate device development and create an ecosystem that fosters the development of devices to better serve people with rare diseases. Due to limited resources, this survey involved clinicians who have a working relationship with FDA and NCATS, principally working in the academic setting. However, these clinicians may have a unique understanding of the regulatory and research ecosystem with respect to medical product development. While our sample over-represents clinicians from academic medical centers, people with rare diseases also are more likely to look to these centers for disease-specific expertise. We recognize that the survey does not engage patient input regarding medical device needs. Despite these limitations, the study not only achieved its primary purpose of verifying unmet medical device needs for people with rare diseases but also verified the magnitude and heterogeneity of these needs.

In addition to the insights shared throughout this report, the data will be made public so that other stakeholders can ascertain additional needs of the rare disease population. For example, it will be important to collect patient perspectives to address their unmet device needs. Future efforts to assess the needs in this area may dive deeper, expand the scope of the evaluation, and reach out to a broader audience to solicit input and advice. The work ahead will require sustained and focused efforts to create an environment in which device development and clinical introduction can be accelerated to meet the critical medical device needs of the 30 million rare disease patients in the United States. This needs assessment provides meaningful documentation about these compelling needs and certifies the agencies' commitment to work with stakeholders in spurring additional rare disease public health action.

APPENDICES

Appendix A: Survey Questionnaire

Appendix B: Expanded Methodology

Appendix C: General Device Needs for Rare Disease Patients

Appendix D: Rare Diseases Specified by Respondents

Appendix E: Diagnostic Device Suggestions for Specified Rare Diseases

Appendix F: Therapeutic Device Suggestions for Specified Rare Diseases

Appendix G: Limitations to Current Diagnostic Devices

Appendix H: Limitations to Current Therapeutic Devices

Appendix I: Challenges with Diagnosing and Treating Pediatric Rare Disease Patients

Appendix J: Acknowledgments

APPENDIX A: SURVEY QUESTIONNAIRE

MODULE OPEN: ALL RESPONDENTS

///ASK ALL

1. OPEN_INTRO1 **Thank you for participating in the Rare Disease Device Needs Survey. The goal of this survey is to identify needs and gaps related to medical devices and tests used in the diagnosis and/or treatment of rare diseases. The information you provide will help the FDA and NIH to evaluate unmet medical device needs in the diagnosis and/or treatment of rare diseases. Your responses will make a valuable contribution to research on rare diseases.**

<u>Your Confidentiality is Protected</u>. Any information that would let someone identify you will be kept private. Your responses to this survey are completely confidential. In addition, survey data will only be reported in aggregate form so that no one will be able to identify you from your responses.

<u>Your participation is voluntary</u>. For most people, the survey will take 15 to 30 minutes, but it may take longer depending on your responses. You can save your responses at any point and return to complete the survey later.

<u>Instructions:</u>
Please read the following instructions before beginning this survey:

1. **TO MOVE FORWARD: Click on the "NEXT" button located at the bottom of the page to save your responses and continue to the next page.**
2. **TO MOVE BACK: Use the "PREVIOUS" button located at the bottom of the page to view your responses on a previous page. You may change your answers to previously entered responses.**
3. **You will be able to exit at any point and re-enter where you left off by clicking the "SAVE AND EXIT SURVEY" button.**
4. **DO NOT use the back button of your browser to return to the previous page. Using your browser's back button may cause you to exit the survey, and your responses will be lost.**

Please note: If you close or exit the survey without clicking the "SAVE AND EXIT SURVEY" button first, you will need to wait 10 minutes to re-enter the survey, and you will need to re-enter your response to the question where you exited the survey.

1. START SURVEY

///ASK IF OPEN_INTRO2 = 1 (continuing with survey)

2. EXPERIENCE1 **For the purposes of this survey, a rare disease is defined as a disease or condition with a prevalence of (i.e., that currently affects) fewer than 200,000 persons in the United States. Examples of some rare diseases that you might know about are: Sickle Cell Disease, Cystic Fibrosis, Progeria, Gaucher's Disease, Huntington's Disease, Alpha-1-Antitrypsin Deficiency, Multiple Myeloma, and Pancreatic Cancer.**

Have you ever had direct experience diagnosing or treating any patients with a rare disease? Please be liberal with what you consider a rare disease. Later in the survey, you will be able to provide us with the names of these disease(s).

1. **Yes**
2. **No**

///ASK IF EXPERIENCE1 = 2, 99 (no direct diagnosis or treatment experience with rare disease populations)

3. EXPERIENCE2 **Would you say that you are knowledgeable about the diagnosis or treatment of any rare diseases—for example, based on the literature you have read, conferences or meetings you have attended, etc.?**

1. **Yes**
2. **No**

///ASK IF EXPERIENCE1 = 1 OR EXPERIENCE2 = 1 (has direct diagnosis or treatment experience with rare disease populations or is knowledgeable about same)

4. DIAGDEVSAT **Overall, how satisfied are you with the devices or tests currently available to you for diagnosing rare diseases? Please consider everything from common everyday devices or tests to disease-specific devices or tests.**

1. **Very satisfied**
2. **Somewhat satisfied**
3. **Neutral**
4. **Somewhat dissatisfied**
5. **Very dissatisfied**

///ASK IF EXPERIENCE1 = 1 OR EXPERIENCE2 = 1 (has direct diagnosis or treatment experience with rare disease populations or is knowledgeable about same)

5. THERDEVSAT **Overall, how satisfied are you with the current range of devices available to you for treating rare diseases? Please consider everything from common everyday devices to disease-specific devices.**

1. **Very satisfied**
2. **Somewhat satisfied**
3. **Neutral**
4. **Somewhat dissatisfied**
5. **Very dissatisfied**

///IF EXPERIENCE1 = 1 OR EXPERIENCE2 = 1 SKIP TO MODULE RD_EXPERIENCE (direct experience or knowledgeable about RD diagnosis or treatment)

///IF EXPERIENCE1 = 2 AND EXPERIENCE2 = 2 SKIP TO MODULE REGULATIONS (no direct experience and not knowledgeable about RD diagnosis or treatment)

///IF EXPERIENCE1 = 99 AND EXPERIENCE2 = 99 SKIP TO MODULE REGULATIONS (skipped both eligibility questions)

END MODULE OPEN

MODULE RD_EXPERIENCE: IF EXPERIENCE1 = 1 OR EXPERIENCE2 = 1

///ASK IF EXPERIENCE1 = 1 (has direct diagnosis or treatment experience with rare disease populations)

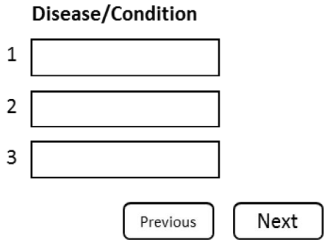
6. DD_NEEDS1 **Of the rare diseases with which you have direct experience (diagnosing or treating), are there any that you believe are in need of new or improved medical devices or tests?**

1. **Yes**
2. **No**

///ASK IF DD_NEEDS1 = 1 (listed direct experience RDs with unmet device needs)

7. DD_NEEDS2 **Thinking of the rare diseases with which you have direct experience, please list up to three that you believe are in need of new or improved medical devices or tests. Please enter the diseases in order of greatest need for a new or improved medical device or test.**

(Please note that if you would like to list more than three diseases, you will have an opportunity to provide that information at the end of the survey.)



This is a required item – it cannot be skipped.

///ASK IF Number of Diseases Listed is 1, 2, 3 (i.e., listed direct experience RDs with unmet device needs)

8. DD_NEEDS3 **For each disease you listed, please indicate:**

- **If the unmet device or test needs are diagnostic, therapeutic, or both;**
- **If the intended patient populations are pediatric, adult, or both; and**
- **All intended settings of use for the needed devices or tests.**

Please select all options that apply.

	Disease/Condition	Unmet Medical Device or Test Needs (Select all that apply)	Populations (Select all that apply)	Intended Settings of Use (Select all that apply)
1	[[DD1_NAME]]	☐ Diagnostic ☐ Therapeutic	☐ Pediatric ☐ Adult	☐ Hospital ☐ Home ☐ Clinic ☐ Other
2	[[DD2_NAME]]	☐ Diagnostic ☐ Therapeutic	☐ Pediatric ☐ Adult	☐ Hospital ☐ Home ☐ Clinic ☐ Other
3	[[DD3_NAME]]	☐ Diagnostic ☐ Therapeutic	☐ Pediatric ☐ Adult	☐ Hospital ☐ Home ☐ Clinic ☐ Other

Previous Next

This information is required – respondent cannot continue if diagnostic need and therapeutic need are both left blank.

///ASK IF Number of Diseases Listed is 1, 2, 3 (i.e., listed direct experience RDs with unmet device needs)

9. DD_NEEDS4 **For each disease you listed, please also indicate:**

- **How many patients you have had experience diagnosing, and**
- **How many patients you have had experience treating.**

	Disease/Condition	Patients Diagnosed	Patients Treated
1	[[DD1_NAME]]	0	0
2	[[DD2_NAME]]	0	0
3	[[DD3_NAME]]	0	0

Previous Next

This information is required – respondent cannot continue if number diagnosed and number treated are both left blank.

///ASK IF EXPERIENCE2 = 1 (knowledgeable about diagnosis or treatment of rare disease populations)

10. KD_NEEDS1 **Of the rare diseases about which you are knowledgeable (regarding diagnosis or treatment), are there any that you believe are in need of new or improved medical devices or tests?**

1. **Yes**
2. **No**

///ASK IF KD_NEEDS1 = 1 (listed knowledgeable RDs with unmet device needs)

11. KD_NEEDS2 **Thinking of the rare diseases about which you are knowledgeable, please list up to three that you believe are in need of new or improved medical devices or tests. Please enter the diseases in order of greatest need for a new or improved medical device or test.**

	Disease/Condition
1	
2	
3	

Previous Next

This is a required item – it cannot be skipped.

///ASK IF Number of Diseases Listed is 1, 2, 3 (i.e., listed knowledgeable RDs with unmet device needs)

12. KD_NEEDS3 **For each disease you listed on the previous page, please indicate:**

- **If the unmet device or test needs are diagnostic, therapeutic, or both;**
- **If the intended patient populations are pediatric, adult, or both; and**
- **All intended settings of use for the needed devices or tests.**

Please select all options that apply.

	Disease/Condition	Unmet Medical Device or Test Needs (Select all that apply)	Populations (Select all that apply)	Intended Settings of Use (Select all that apply)
1	[[KD1_NAME]]	☐ Diagnostic ☐ Therapeutic	☐ Pediatric ☐ Adult	☐ Hospital ☐ Home ☐ Clinic ☐ Other
2	[[KD2_NAME]]	☐ Diagnostic ☐ Therapeutic	☐ Pediatric ☐ Adult	☐ Hospital ☐ Home ☐ Clinic ☐ Other
3	[[KD3_NAME]]	☐ Diagnostic ☐ Therapeutic	☐ Pediatric ☐ Adult	☐ Hospital ☐ Home ☐ Clinic ☐ Other

Previous Next

This information is required – respondent cannot continue if diagnostic need and therapeutic need are both left blank.

///LOOP: FOR EACH DISEASE X ENUMERATED IN GRID

1.1: Diagnostic device/test or test needs for disease X

///ASK IF DX_DIAGNEED = 1 (New/improved medical devices or tests needed for diagnosis of DX)

13. DX_DIAG_INTRO **The next set of questions will ask about diagnostic device or test needs for [[DX_NAME]].**

1. **CONTINUE**

///ASK IF DX_DIAG_INTRO = 1 (Continuing)

14. DX_DIAG1 **With regard to diagnostic devices or tests, which one of the following is MOST needed to help diagnose [[DX_NAME]]?**

1. **Modification (i.e., physical adaptation) of an existing diagnostic device or test**
2. **Using an existing diagnostic device or test for a different indication (i.e., repurposing)**
3. **Creation of a new diagnostic device or test**

///ASK IF DX_DIAG1 = 1,2,3 (Indicated which type of diagnostic device/test is most needed)

15. DX_DIAG2 $ 500 **Please briefly describe (in two to three sentences) your suggestion to [[modify/repurpose/create]] a diagnostic device or test for [[DX_NAME]]:**

TEXT AREA OPEN-ENDED

///ASK IF DX_DIAG1 = 1,2,3 (Indicated which type of diagnostic device/test is most needed)

16. DX_DIAG3 **How would the availability of this [[modified/repurposed/new]] device or test affect the diagnosis of [[DX_NAME]]? Please select all that apply.**

[SELECT ALL THAT APPLY]

1. **It would make diagnosis quicker**
2. **It would make diagnosis more sensitive**
3. **It would make diagnosis more specific**
4. **It would make diagnosis less cumbersome**
5. **It would make diagnosis less invasive**
6. **Other: SPECIFY**

///ASK IF DX_DIAG1 = 1,2,3 (Indicated which type of diagnostic device/test is most needed)

17. DX_DIAG4 **Overall, what kind of impact would the availability of this [[modified/repurposed/new]] device or test have on the diagnosis of [[DX_NAME]]?**

1. **Breakthrough advancement**
2. **Important incremental improvement**

98. **Don't know**

1.2: Current diagnostic practices for disease X

///ASK IF EXPERIENCE1 = 1 AND DDX_NDIAGNOSED > 1 AND DX_DIAGNEED = 1 (Has direct diagnostic experience with rare disease patients, and indicated new/improved medical devices or tests needed for diagnosis of RD)

18. DX_DIAGEXP1 Do you use any medical devices or tests to diagnose [[DX_NAME]]?

1. **Yes**
2. **No**

///ASK IF DX_DIAGEXP1 = 1 (Using a diagnostic device/test for DX)

19. DX_DIAGEXP2 Which of the following devices or tests do you use to diagnose [[DX_NAME]]? Please select all that apply.
(*Please remember that your responses to this survey are completely confidential. Survey data will only be reported in aggregate form so that no one will be able to identify you from your responses*.)
[SELECT ALL THAT APPLY]

1. **A diagnostic device or test that is FDA-approved/cleared for this indication**
2. **A repurposed diagnostic device or test that is FDA-approved/cleared for a different indication**
3. **A modified (i.e., physically adapted) diagnostic device or test**
4. **A common non-disease–specific device (e.g., x-ray or stethoscope)**
5. **A test developed by a laboratory affiliated with your practice site**
6. **Other: SPECIFY**
98. **Don't know**

///ASK IF DX_DIAGEXP1 = 1 (Using a diagnostic device/test for DX)

20. DX_DIAGEXP3 $ 500 Please briefly describe (in two to three sentences) any limitations in using these device(s) or test(s) to diagnose [[DX_NAME]]:
TEXT AREA OPEN-ENDED

If this is left blank, prompt user: "No text was entered for this question. Are you sure you want to leave this response empty?" with "Yes" and "No" as response buttons. If Yes, continue to next item. If No, return focus to text area.

///ASK IF DX_DIAGEXP1 = 2 (Not using a diagnostic device/test for DX)

22. DX_DIAGEXP5 In general, how else do you diagnose [[DX_NAME]]? Please select all that apply.
[SELECT ALL THAT APPLY]

1. **Symptoms/medical history**
2. **Physical exam**
3. **General lab**
4. **Functional/performance tests**
5. **Imaging**
6. **Genetic tests**
7. **Pathology/biopsy tests**

8. **Other: SPECIFY**

2.1: Therapeutic device/test needs for disease X

///ASK IF DX_THERNEED = 1 (New/improved medical devices needed for treatment of DX)

23. DX_THER_INTRO **The next set of questions will ask about therapeutic device needs for [[DX_NAME]].**

1. **CONTINUE**

///ASK IF DX_THER_INTRO = 1 (Continuing)

24. DX_THER1 **Therapeutic devices are those that are intended to cure, mitigate, or treat a disease. Thinking of medical devices, which one of the following is MOST needed to help treat [[DX_NAME]]?**

1. **Modification (i.e., physical adaptation) of an existing therapeutic device**
2. **Using an existing therapeutic device for a different indication (i.e., repurposing)**
3. **Creation of a new therapeutic device**

///ASK IF DX_THER1 = 1,2,3 (Indicated which type of therapeutic device is most needed)

25. DX_THER2 $ 500 **Please briefly describe (in two to three sentences) your suggestion to [[modify/repurpose/create]] a therapeutic device for [[DX_NAME]]:**

TEXT AREA OPEN-ENDED

If this is left blank, prompt user: "No text was entered for this question. Are you sure you want to leave this response empty?" with "Yes" and "No" as response buttons. If Yes, continue to next item. If No, return focus to text area.

///ASK IF DX_THER1 = 1,2,3 (Indicated which type of therapeutic device is most needed)

26. DX_THER3 **How would the availability of this [[modified/repurposed/new]] device affect the treatment of [[DX_NAME]]? Please select all that apply.**

[SELECT ALL THAT APPLY]

1. **Prolong survival**
2. **Restore/replace organ function**
3. **Provide temporary relief**
4. **Improve quality of life**
5. **Other: SPECIFY**

///ASK IF DX_THER1 = 1,2,3 (Indicated which type of therapeutic device is most needed)

27. DX_THER4 **Overall, what kind of impact would the availability of this [[modified/repurposed/new]] device have on the treatment of [[DX_NAME]]?**

1. **Breakthrough advancement**
2. **Important incremental improvement**

98. **Don't know**

///ASK IF EXPERIENCE1 = 1 AND DDX_NTREATED > 1 AND DX_THERNEED = 1 (**Has direct therapeutic experience with rare disease patients**, and indicated new/improved medical devices needed for treatment of DX)

28. DX_THEREXP1 **Do you use any medical devices to treat [[DX_NAME]]?**

1. **Yes**
2. **No**

///ASK IF DX_THEREXP1 = 1 (Using a therapeutic device for DX)

29. DX_THEREXP2 **Which of the following devices do you use to treat [[DX_NAME]]? Please select all that apply.**
(*Please remember that your responses to this survey are completely confidential. Survey data will only be reported in aggregate form so that no one will be able to identify you from your responses*.)
[SELECT ALL THAT APPLY]

1. **A therapeutic device that is FDA-approved/cleared for this indication**
2. **A repurposed therapeutic device that is FDA-approved/cleared for a different indication**
3. **A modified (i.e., physically adapted) therapeutic device**
4. **A common non-disease–specific device (e.g., a transcutaneous electrical nerve stimulator, splint, or contact lens)**
5. **Other: SPECIFY**
98. **Don't know**

///ASK IF DX_THEREXP1 = 1 (Using a therapeutic device for DX)

30. DX_THEREXP3 $ 500 **Please briefly describe (in two to three sentences) any limitations using these device(s) to treat [[DX_NAME]]:**
TEXT AREA OPEN ENDED

If this is left blank, prompt user: "No text was entered for this question. Are you sure you want to leave this response empty?" with "Yes" and "No" as response buttons. If Yes, continue to next item. If No, return focus to text area.

///ASK IF DX_THEREXP1 = 2 (Not currently using a therapeutic device for DX)

32. DX_THEREXP5 **In general, how else do you treat [[DX_NAME]]? Please select all that apply.**
[SELECT ALL THAT APPLY]

1. **Does not apply; no treatment exists**
2. **Drugs**
3. **Biological product**
4. **Genetic product**
5. **Medical food**
6. **Other: SPECIFY**

///ASK IF Number of Diseases Listed = 2, 3

32NEW. DX_ Thank you for your input on [[Disease 1]]. Do you want to complete a similar series of questions for [[Disease 2/3]] at this time? If not, you will have a chance to respond to the questions at the end of the survey.

1. **Yes //REPEAT SERIES for Disease 2, then re-ask this for Disease 3 if N_REDNUM = 3//**

2. No

PROGRAMMER: If RDENUM=3 and the respondent selects YES for DX_THEREXP6 for Disease 2, proceed through the loop for Disease 2 then ask DX_THEREXP6 again for Disease 3. If RDENUM=3 and the respondent selects NO for DX_THEREXP6 in response to Disease 3, immediately repeat DX_THEREXP6 for Disease 3.

///END LOOP: FOR EACH DISEASE X ENUMERATED IN GRID

1.

END MODULE RD_EXPERIENCE: IF EXPERIENCE1 = 1 OR EXPERIENCE2 = 1

MODULE TOP_CATEGORIES: IF EXPERIENCE1 = 1 OR EXPERIENCE2 = 1

///ASK IF EXPERIENCE1 = 1 OR EXPERIENCE2 = 1 (has direct diagnosis or treatment experience with rare disease populations or is knowledgeable about same)

33. TC_INTRO1 **For the following questions, please think of the needs of all rare disease populations about which you are knowledgeable (not just those patients you may have personally diagnosed or treated, if any).**

1. CONTINUE

///ASK IF TC_INTRO1 = 1 (Continuing)

34. TC_NEEDS1 **The following questions ask about <u>GENERAL device or test needs</u> for patients with rare diseases. These are <u>broad categories</u> of device or test needs.**

Would you consider each of the following to be a GENERAL device or test need for patients with rare diseases?

	Yes	No	Don't Know
Pediatric implants that grow with a child	O	O	O
Devices/tests that are specific for diagnosing genetic disorders	O	O	O
Pediatric intrathecal ports for drug delivery	O	O	O

///ASK IF TC_INTRO1 = 1 (Continuing)

35. TC_NEEDS2 **Please list up to three other <u>GENERAL device or test needs</u> that would have the greatest impact on patients with rare diseases (starting with the most important).**

General Device/Test Need

1 [ ]

2 [ ]

3 [ ]

Previous Next

///ASK IF TC_NEEDS_ENUM IN (1, 2, 3) (Listed any general device/test needs)

36. TC_NEEDS3 **For each general device/test need you listed on the previous page, please indicate:**

- **The device/test type (diagnostic, therapeutic, or both);**
- **The target populations (pediatric, adult, or both); and**
- **All intended settings of use for the needed devices or tests.**

Please select all options that apply. You will only be asked one follow-up question for each need listed in this table.

	General Device/Test Need	Device/Test Type (Select all that apply)	Target Population (Select all that apply)	Intended Setting of Use (Select all that apply)
1	[[TC1_NAME]]	☐ Diagnostic ☐ Therapeutic	☐ Pediatric ☐ Adult	☐ Hospital ☐ Home ☐ Clinic ☐ Other
2	[[TC2_NAME]]	☐ Diagnostic ☐ Therapeutic	☐ Pediatric ☐ Adult	☐ Hospital ☐ Home ☐ Clinic ☐ Other
3	[[TC3_NAME]]	☐ Diagnostic ☐ Therapeutic	☐ Pediatric ☐ Adult	☐ Hospital ☐ Home ☐ Clinic ☐ Other

Previous Next

This information is required – respondent cannot continue if diagnostic need and therapeutic need are both left blank.

///LOOP: FOR EACH GENERAL DEVICE/TEST NEED X ENUMERATED IN GRID (X = 1 TO TC_NEEDS_ENUM)

37. TCX_IMPACT $ 500 **What rare disease(s) would be impacted if the need for [[TCX_NAME]] was addressed?**

TEXT AREA OPEN ENDED

If this is left blank, prompt user: "No text was entered for this question. Are you sure you want to leave this response empty?" with "Yes" and "No" as response buttons. If Yes, continue to next item. If No, return focus to text area.

///END LOOP: FOR EACH GENERAL DEVICE/TEST NEED X ENUMERATED IN GRID

END MODULE TOP_CATEGORIES: IF EXPERIENCE1 = 1 OR EXPERIENCE2 = 1

MODULE REGULATIONS: ALL RESPONDENTS

///ASK ALL

38. IMPED **To what extent do you think each of the following may be an impediment to the development of medical devices or tests for rare diseases?**

	Large Extent	Moderate Extent	Small Extent	Not an Impediment	Don't Know
Cost of development	o	o	o	o	o
Not profitable to industry	o	o	o	o	o
Time required for development	o	o	o	o	o
Need for clinical trials	o	o	o	o	o
Government regulations	o	o	o	o	o
Small, heterogeneous population	o	o	o	o	o
Technology limitations	o	o	o	o	o
Liability during a clinical trial	o	o	o	o	o
Pathophysiology of the disease or disease mechanism is not yet known	o	o	o	o	o
Other: SPECIFY	o	o	o	o	o

///ASK ALL

39. HUD1

A Humanitarian Use Device (HUD) is a medical device intended to treat or diagnose a disease or condition affecting fewer than 4,000 individuals in the United States per year. A Humanitarian Device Exemption (HDE) is the FDA marketing application that modifies/reduces certain data requirements for the developers of a HUD.

Before you took this survey, were you aware of the HUD/HDE pathway?

1. **Yes**
2. **No**

///ASK IF HUD1 = 1 (Previously aware of HUD)

40. HUD2 **How helpful do you think the HUD/HDE pathway is in meeting the needs of diagnosing or treating patients with rare diseases?**

1. **Very helpful**
2. **Helpful**
3. **Somewhat helpful**
4. **Not helpful**

98. Don't know

///ASK IF HUD1 = 1 (Previously aware of HUD)

42. HUD3 **Have any of the following presented a challenge to you in using Humanitarian Use Devices? Please select all that apply.**

[SELECT ALL THAT APPLY]

1. **Reimbursement**
2. **Institutional Review Board (IRB) constraints**
3. **Access to humanitarian use devices**
4. **Safety**
5. **Less than expected benefit to the patient**
6. **Patient eligibility**
7. **Other: SPECIFY**

END MODULE REGULATIONS: ALL RESPONDENTS

MODULE DEMOGRAPHICS: ALL RESPONDENTS

///ASK IF EXPERIENCE1 = 1 OR EXPERIENCE2 = 1 (has direct diagnosis or treatment experience with rare disease populations or is knowledgeable about same)

43. NPATIENTS **In total, how many rare disease patients have you personally seen in the past 2 years?**

1. **None**
2. **1 to 20**
3. **21 to 50**
4. **51 to 99**
5. **100 to 499**
6. **500 or more**

///ASK IF NPATIENTS = 2,3,4,5,6 (Seen 1 or more RD patients in past 2 years)

44. PEDPATIENTS **What proportion of these patients were 21 years old or younger?**

1. **None**
2. **Fewer than half**
3. **About half**
4. **More than half**
5. **All**

///ASK IF PEDPATIENTS = 2,3,4,5 (At least some pediatric RD patients)

45. PEDCHALL $ 500 **Please briefly describe (in two to three sentences) any challenges you have faced in treating or diagnosing rare diseases in patients who are 21 years old or younger.**

TEXT AREA OPEN-ENDED

If this is left blank, prompt user: "No text was entered for this question. Are you sure you want to leave this response empty?" with "Yes" and "No" as response buttons. If Yes, continue to next item. If No, return focus to text area.

///ASK ALL

46. SPEC **Please select the choice(s) below that best describe your specialty or sub-specialty. If you have more than one specialty, please select all that apply.**

[SELECT ALL THAT APPLY]

Allergy and Immunology
Anesthesiology
Cardiology
Colon and Rectal Surgery
Dermatology
Diagnostic Radiology
Emergency Medicine
Endocrinology
Family Medicine
Gastroenterology
Geriatrics
General Medicine
Internal Medicine
Medical Genetics
Nephrology
Neurology
Neurological Surgery
Nuclear Medicine
Obstetrics and Gynecology
Oncology
Ophthalmology
Orthopaedic Surgery
Otolaryngology
Pathology
Pediatrics
Physical Medicine and Rehabilitation
Physiatry
Plastic Surgery
Podiatry
Pulmonology
Preventive Medicine
Psychiatry
Radiation Oncology
Radiology
Rheumatology
Surgery
Thoracic Surgery
Urology
Other: Specify

///ASK ALL

47. SETTING **In which setting do you provide care? Please select all that apply.**

[SELECT ALL THAT APPLY]

1. Academic clinical center
2. Non-academic hospital
3. Patient's home
4. Group practice
5. Single practitioner
6. Other: SPECIFY

///ASK ALL

48. YRSFIELD **In total, how many years have you practiced in your field (i.e., including residency or fellowship)?**

1. I have never practiced in my field
2. Less than 1 year
3. 1 year to less than 5 years
4. 5 years to less than 10 years
5. 10 years or more

///ASK ALL

49. DEV_DEVELOP **Have you ever been involved in the development of a medical device or test?**

1. Yes
2. No

///ASK ALL

50. DEV_TRIAL **Have you ever been involved in any medical device trials?**

1. Yes
2. No

///ASK IF DD_NEEDS_ENUM = 2, 3 (Listed multiple diseases) AND DX_THEREXP6=2 (declined to answer earlier)

53. DD_NEEDS_XTRA **Earlier you listed [Disease 2/3] as a rare disease that you believe is in need of a new or improved medical device or test. Would you like to answer a series of questions on diagnosing and/or treating [Disease 2/3]?**

1. Yes
2. No

If Number of Diseases Listed=3 and the respondent selects YES for DD_NEEDS_EXTRA for Disease 2, proceed through the loop for Disease 2 then ask DD_NEEDS_EXTRA again for Disease 3. If Number of Diseases Listed=3 and the respondent selects NO for DD_NEEDS_EXTRA in response to Disease 2, immediately repeat DD_NEEDS_EXTRA for Disease 3.

///ASK IF KD_NEEDS_ENUM = 2, 3 (Listed multiple diseases) AND D2_THEREXP6=2 (declined to answer earlier)

54. KD_NEEDS_XTRA **Earlier you listed [Disease 2/3] as a rare disease about which you are knowledgeable and believe is in need of a new or improved medical device or test. Would you like to answer a series of questions related on diagnosing and/or treating [Disease 2/3]?**

1. Yes

2. No

If Number of Diseases Listed=3 and the respondent selects YES for KD_NEEDS_EXTRA for Disease 2, proceed through the loop for Disease 2 then ask KD_NEEDS_EXTRA again for Disease 3. If Number of Diseases Listed=3 and the respondent selects NO for KD_NEEDS_EXTRA in response to Disease 2, immediately repeat KD_NEEDS_EXTRA for Disease 3.

MODULE CLOSE: ALL RESPONDENTS

///ASK ALL

52. THANK **Thank you for your participation in this survey. Your responses have made a valuable contribution to our research.**

If you have any questions about FDA's rare disease medical device needs assessment (of which this survey is a part) or additional comments on medical device needs for rare diseases, please contact FDA at rarediseaseproject@fda.hhs.gov, or call 301-796-8660 and mention "Needs Assessment."

For more information about the Food and Drug Administration, Office of Orphan Product Development, please visit http://www.fda.gov/orphan.

For more information about the National Center for Advancing Translational Sciences, Office of Rare Diseases Research and the Genetic and Rare Diseases Information Center (GARD), visit http://rarediseases.info.nih.gov/gard.

APPENDIX B: EXPANDED METHODOLOGY

This section outlines the methodology used in developing, administering, and analyzing the results of the Web survey. The Food and Drug Administration (FDA) and the National Center for Advancing Translational Sciences (NCATS)/Office of Rare Diseases Research (ORDR) at the National Institutes of Health (NIH) contracted with ICF, a global consulting and technology services firm, for survey development, design, implementation, data processing, and report drafting.

Stakeholder Consultations

To conduct the needs assessment, FDA's Office of Orphan Products Development (OOPD), Center for Devices and Radiological Health (CDRH), and Office of Planning, together with NCATS/ORDR, formed a Needs Assessment Working Group (NAWG). The NAWG planned a collaborative effort to reach out to various rare disease and pediatric stakeholders, including researchers, clinicians (including physicians and non-physician clinicians who work with patients), patients, patient advocacy organizations, and members of industry. Besides FDA and NCATS/ORDR staff, stakeholders from the American Academy of Pediatrics, the American Medical Association, the National Organization for Rare Diseases, and AdvaMed participated in a project kickoff meeting on October 30, 2013, during which the agencies conducted expert solicitation on the goals of the project, desired outcomes, key objectives, approaches to obtaining data, and complexities and obstacles. These stakeholders were also invited to provide additional input to the NAWG to guide the project. On January 8, 2014, FDA held a public workshop entitled Complex Issues in Developing Medical Devices for Pediatric Patients Affected by Rare Diseases. During this workshop, the NAWG provided an overview of the Medical Devices for Rare Diseases Needs Assessment Project and solicited feedback. The NAWG continued to use post-meeting input from stakeholders and public meeting attendees to inform and focus their approach toward the needs assessment.

Survey Development

The development of the survey was an iterative and collaborative process that took place from April 2014 through October 2015 and included several planning meetings, cognitive interviews, and usability testing.

Survey Framework and Questionnaire Development

The NAWG held a brainstorming session with its research contractor on April 2, 2014, to discuss the overall survey framework. Additional meetings were held throughout the questionnaire development and revision process, from April through September 2014. The survey was designed to capture information from clinicians to

- identify unmet medical device needs for rare diseases;
- understand the extent of the need in rare disease populations;
- generate meaningful data to inform patients, practitioners, and developers working to address those unmet needs.

To do this, the survey included closed- and open-ended questions and solicited information on both diagnostic and therapeutic needs. Although it was anticipated that the audiences surveyed would be knowledgeable on rare disease populations, the survey separated out clinicians with

direct experience working with rare disease populations from those with no direct experience working with rare disease populations but knowledge about rare diseases. This was done to enable comparative analyses to examine differences between the two groups once all data had been collected. All respondents with experience with rare disease patients or knowledge of rare diseases were asked about (1) satisfaction with current diagnostic and therapeutic devices; (2) unmet diagnostic and therapeutic device needs for up to three specific rare diseases identified by each respondent; and (3) unmet diagnostic and therapeutic device needs for rare disease populations in general. Those with direct experience with rare disease patients were also asked about current diagnostic and therapeutic practices for specific rare diseases identified by each respondent.

In addition, the survey included questions that could be answered by all respondents, regardless of their experience with rare disease populations, which addressed impediments to increased medical device development and testing and familiarity and experience with Humanitarian Use Devices (HUDs). Finally, all respondents were asked about their clinical background and experiences, including the number and type of patients seen, clinical specialty, setting(s) for care, years of clinical experience, and involvement in the development of a medical device and/or medical device trials.

Cognitive Interviews and Stakeholder Feedback

Prior to fielding, the entire survey questionnaire was cognitively tested with nine physicians from the public identified by the NAWG to ensure clarity in the survey questions, question order and instructions. Each of the physicians had experience with rare disease populations or knowledge of medical devices used to diagnose or treat patients with rare diseases. All nine physicians worked in the Washington, DC metropolitan area. The interviews were conducted between November 13 and December 18, 2014. The survey was revised on the basis of these cognitive interviews; such revisions included clarifying some of the questions, adding emphasis on the confidentiality of the survey, and simplifying some aspects of the survey to reduce the burden on the survey respondents. In addition, the survey was reviewed by members of AMA in October 2014. The overall structure of the survey, as presented in Figure 1, did not change.

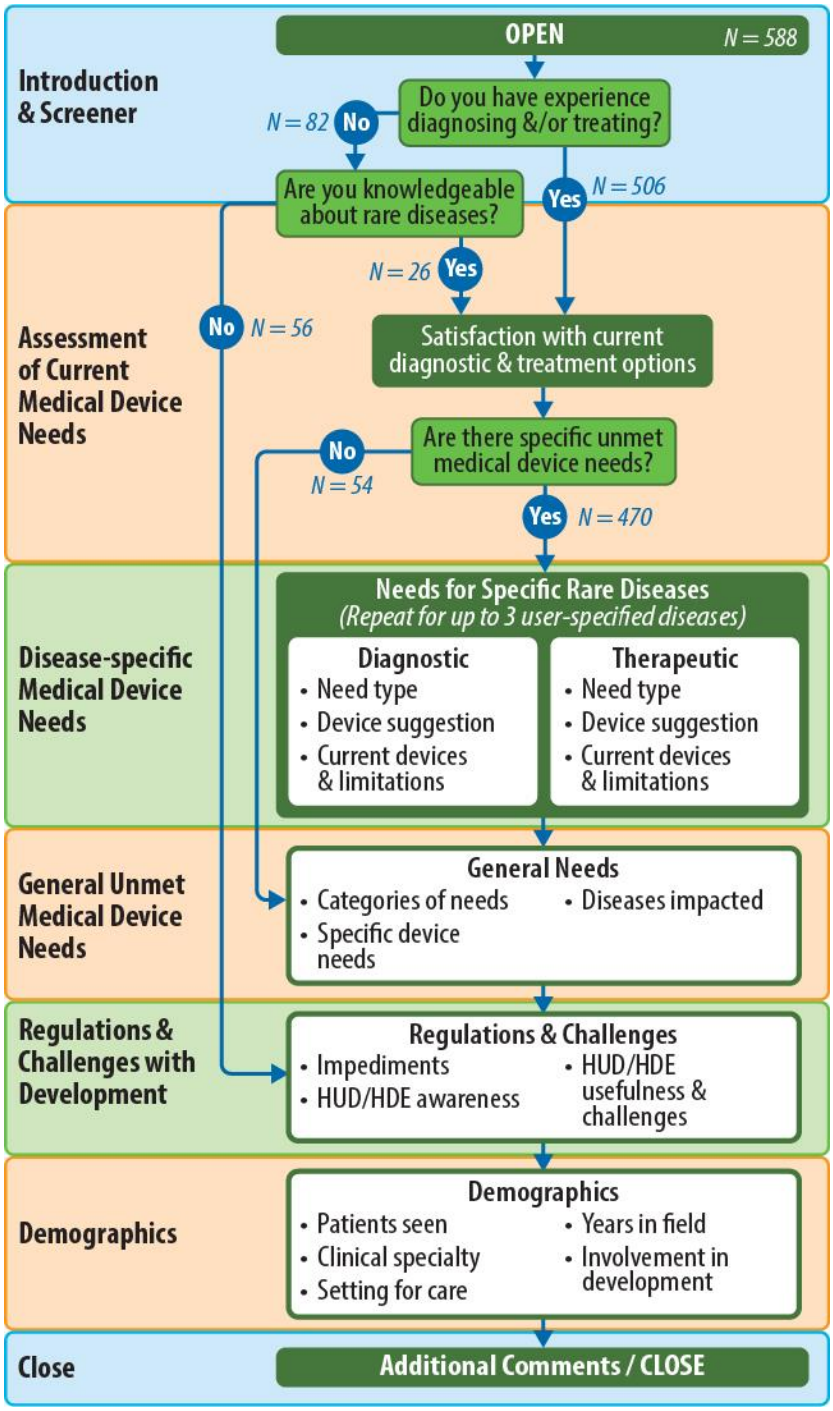
Web Programming and Usability Testing

Web programming for the survey began in March 2015. The survey was programmed to be accessible on computers, as well as tablets. Once programmed, the NAWG tested the survey on both types of devices before conducting usability testing in July 2015. During the usability testing, some FDA physician employees found the survey to be lengthy and burdensome. To address this, the NAWG and its contractor discussed several solutions. Ultimately,

- additional text was added to the landing page to emphasize that the clinician's participation is voluntary and that the clinician could start, stop, and reenter the survey at another time;
- new skip patterns were added to the series of questions about user-specified rare diseases, allowing respondents to complete the questions related to their second and/or third diseases entered at the end of the survey rather than immediately following the questions pertaining to their first disease entered, or to skip the questions for the second and/or third disease entirely.

The final survey organization and primary skip patterns are shown in Figure 1.

Figure 1: Structure of the Clinician Survey



Survey Fielding

FDA and its contractor independently sought and received institutional review board approval for the survey prior to fielding. The survey was fielded to members of four clinician groups whose members were directly accessible and had experience or knowledge in the areas of medical devices and/or rare diseases. To better understand and address the unique needs of pediatric patients, two of the selected groups included clinicians with predominant training and experience with pediatric patients. Brief descriptions of the four groups appear below:

FDA CDRH Advisory Committee. This Committee is made up of 18 panels primarily consisting of expert physicians and other clinicians who provide advice to the FDA about issues related to the safety and effectiveness of medical devices.

FDA Pediatric Advisory Committee. This Committee, primarily consisting of expert physicians, advises and makes recommendations to the FDA on a variety of pediatric issues and concerns, including research priorities; ethics, design, and analysis of clinical trials; and labeling disputes or changes in labels.

FDA Pediatric Device Consortia. The Consortia includes physicians and other experts in medical device development who work together to promote the development of medical devices for children.

NCATS/ORDR Rare Diseases Clinical Research Network (RDCRN) Program. The RDCRN Program provides support for clinical studies and facilitates collaboration, study enrollment, and data sharing to advance research on rare diseases. Through its network, physician scientists and their multidisciplinary teams work together with representatives of patient advocacy groups to advance rare disease clinical research and investigate new treatments for patients.

Pilot Test

To ensure the survey functioned properly, it was piloted with a subset of the members of the FDA CDRH Advisory Committee. The pilot included the CDRH Advisory Committee members who were active in 2014. All communications for the survey were transmitted by e-mail. The director for the CDRH Advisory Committee sent a pre-notification e-mail prior to the invitations, as well as a notification of a deadline extension for completing the survey that was sent shortly before the survey was originally scheduled to close. The remaining survey communications, including the survey invitations and several reminders, were sent by ICF using an e-mail account used exclusively for this survey project.

The pre-notification e-mail described the nature, purpose, and importance of the survey effort, as well as alerting the clinician to expect the e-mail invitation from ICF the following day. The invitation referenced the pre-notification e-mail from the director, described the nature and purpose of the survey, and provided a personalized URL to use in completing the survey. The reminders sent by ICF each contained a personalized survey URL, as well as a brief description of the survey and its importance. Reminders were sent only to those clinicians who had not yet completed the survey. The deadline extension notification e-mail sent by the director of the CDRH Advisory Committee was sent to all members to maintain the anonymity of those who had and had not yet completed the survey and did not contain the survey URL. All survey communications included information for contacting FDA regarding the purpose or nature of the survey and for contacting the contractor with questions about accessing the survey.

The pilot survey opened on September 23, 2015, and closed on October 18, 2015. Four reminder e-mails were sent throughout the fielding period. The use of a personalized survey URL allowed clinicians to stop and re-start the survey at the most recent question completed at will throughout the fielding period. An informational phone line and e-mail account at FDA was maintained throughout the fielding period to address questions about the nature or purpose of the survey. A telephone and e-mail help desk was maintained by the contractor throughout the fielding period as well, to assist clinicians with questions or concerns about accessing and completing the survey. The help desk offered a toll-free telephone number and an e-mail account and was staffed during standard business hours for the Eastern Time Zone.

The data were analyzed following the pilot survey to look for signs of confusing questions or instructions and any previously undetected programming issues. No issues were identified. No changes were made to the survey instrument or the fielding procedures following the pilot test.

First Wave

The full implementation for first wave included the 727 clinicians who had served on the CDRH Advisory Committee in the past, excluding those surveyed during the pilot test. The methodology followed that used for the pilot test. The pre-notification e-mails were sent by the director of the CDRH Advisory Committee on November 3, 2015, and the invitations were sent by ICF on November 4, 2015. The survey closed on December 5, 2015. Six periodic reminder e-mails were sent by ICF, as well as a notification of a deadline extension for completing the survey that was sent by the director of the CDRH Advisory Committee shortly before the survey was originally scheduled to close. All communications were identical to those used during the pilot test.

Second Wave

The second wave of the survey included the clinicians from the NCATS/ORDR Rare Diseases Clinical Research Network, the FDA Pediatric Device Consortia, and the FDA Pediatric Advisory Committee. The methodology followed that used for the pilot test and first wave. The pre-notification e-mails were sent by the directors of the three organizations on January 26 and 27, 2016. The invitations were sent by ICF on January 28, and the survey closed on February 29. The second wave included five periodic reminder e-mails, sent by ICF. The directors of the three organizations sent a notification of a deadline extension for completing the survey shortly before the survey was originally scheduled to close, as was done with the pilot test and first wave. All communications were identical to those used during the pilot test and first wave.

Response Rate

In total, 1,342 individuals were successfully invited to participate (that is, although 1,381 individuals were invited, 39 invitations bounced back), of whom 588 completed the survey in whole or in part, for an overall response rate of 44%. Table 1 presents an overview of the response rate data from each of the four groups surveyed. Response rate was calculated by dividing the number of fully or partially completed surveys by the total number of individuals surveyed, excluding respondents whose invitations had bounced back because those clinicians never received the survey. Respondents were marked refusals when they contacted the help desk and asked to be removed from the sample, oftentimes indicating that they were not clinicians or did not possess the knowledge needed to complete the survey.

Table 1: Sample Sizes and Response Rates

Clinician Group	Sample Size	Bounce-Backs	Refusals	Respondents*			Response Rate
				Direct Experience	Knowledge Only	No Experience or Knowledge	
CDRH	857	30	5	251	20	54	39%
PAC	26	0	0	15	0	0	58%
PDC	63	0	0	40	1	1	67%
RDCRN	435	9	0	200	5	1	48%
Total	1,381	39	5	506	26	56	44%

*These figures include both completed and partially completed surveys.

To be considered a completed survey, respondents with direct experience with rare disease populations or knowledge of rare diseases must have completed the applicable diagnostic- and/or treatment-related questions for at least one rare disease, leaving no more than one question blank in each series. The primary purpose of the survey was to gather the information contained in this series of questions, hence they were of the most importance in determining the completeness of the data. Respondents were allowed to leave one question blank in each series since it is possible that they left the question pertaining to suggestions for a new device blank because they had no suggestions to offer. For those without direct experience or knowledge, respondents must have completed all applicable survey questions to be considered complete. The minimum number of survey items required for respondents without direct experience or knowledge is nine questions, all of which were closed-ended. To be considered a partially completed survey, the respondent must have completed the opening screener question(s) about direct experience with rare disease populations and knowledge of rare diseases, plus at least one applicable survey question on the needs of medical devices for rare disease. Clinicians who completed only the opening screener question(s) were considered non-respondents and their data were excluded from the analysis.

Data Preparation and Analysis

Several preliminary data cleaning and data processing steps were taken prior to beginning the data analysis. After removing the data from refusals and those cases that did not meet the minimum threshold required to be considered a partially or fully completed survey, the analysis for each survey item included all respondents who completed the question—regardless of whether the respondent submitted a completed or a partially completed survey. Of note, most questions in the survey could be skipped, so the sample size (N) for each survey question varied on the basis of both the skip patterns and the ability of respondents to skip the question. For this reason, the sample size for each question varies considerably and is reported in the figure headings for easy reference.

Data Processing

Although the data from those with direct experience diagnosing or treating patients with rare diseases and respondents with knowledge of rare diseases were captured separately, the responses from both groups were similar throughout and the group of respondents with knowledge but not

direct treatment experience was small (N = 26). Because of this, the data for the two groups of respondents were combined and are reported together throughout this report. However, those without direct experience were not asked questions about current diagnostic and therapeutic practices.

For the survey items covering unmet medical device and test needs for user-specified rare diseases, respondents were asked to enter the names and answer questions related to up to three rare diseases, in order of greatest need. Respondents were required to answer only the questions for the first disease they entered and were given the option to skip the related questions for the second and third diseases they named, so the sample size for responses varies. The analysis for these questions was done at the disease level rather than the respondent level to ensure that all diseases were analyzed together rather than entering separate analyses for the first, second, and third diseases. Doing so required the creation of a separate data file that combined the data from the first, second, and third user-specified rare diseases into one category of disease-related information.

A separate data file was also created for the survey items covering general medical device needs for rare diseases, using the same procedures that were used for the data file on user-specified rare diseases. As with the section on user-specified rare diseases, respondents could enter the names and answer related questions for up to three general device needs. Unlike the section on user-specified rare diseases, respondents were not given the option to skip the questions related to the second and third general device needs they entered.

Prior to the analysis, experts from the NAWG reviewed the list of user-specified rare diseases to ensure the diseases qualified as rare diseases under the definition used for the survey (i.e., a disease or condition with a prevalence of fewer than 200,000 persons in the United States). The device suggestions provided by the respondents were reviewed in addition to the disease name to ensure that a disease not generally fitting the definition but that may potentially be considered an orphan subset of that disease could be categorized appropriately. Diseases were classified as "definitely rare," "maybe rare," or "not rare." Diseases classified in the maybe rare category were generally those for which determinations of subset were not able to be made based on disease name or the device suggestion. After analyzing the data from diseases categorized as rare and those categorized as maybe rare for several key survey items, the NAWG decided to analyze the two categories together; responses were similar between the two groups for all questions examined. In total, 828 of the diseases were classified as rare, 89 were classified as maybe rare, and 149 were classified as not rare.[23]

The NAWG also categorized the rare diseases according to the medical specialty to which they pertain. The procedures used for this were similar to those used for the categorization of disease rarity—the device suggestion was reviewed in addition to the disease name to gain additional clarity on the responses being categorized.

[23] These percentages are based on the total number of responses entered to the disease questions, not taking into account any diseases that were entered by more than one respondent. Thus, diseases entered multiple times are counted as separate cases for each time they were entered.

Analysis Procedures

The analysis discussed in this report includes data from both closed- and open-ended survey items. For the closed-ended questions, the analysis includes frequencies and crosstabs. For the open-ended questions, and for the "other, specify" sections of some closed-ended survey items, responses were coded using qualitative analysis techniques that examine the response for common themes across the responses to each survey question.

Comparison Used Throughout Report

Separate analyses of respondents with a pediatric focus (i.e., those who had a pediatric specialty and/or significant experience with pediatric patients) were conducted to examine differences among this key group of interest compared to all respondents. In total, 33% of respondents (N = 192) were included in the category of clinicians with a pediatric focus. Two survey items were used to distinguish clinicians with a pediatric focus. The first asked respondents to indicate their clinical specialty. Eighty-nine respondents (15% of all respondents) either selected the pediatrics category or were assigned to it on the basis of FDA's review of their open-ended response after selecting "other" for the clinical specialty question.[24] A second question was asked only of those respondents who had seen rare disease patients during the previous two years; respondents were asked to specify the proportion of their patients over the previous two years who were aged 21 or younger. In response to this question, 179 respondents (30% of all respondents) indicated that half or more of their patients were aged 21 or younger. Respondents were considered clinicians with a pediatric focus if they met at least one of these two criteria. In total, 76 respondents met both criteria, 13 respondents reported they had a clinical specialty in pediatrics, and 103 respondents reported that half or more of their patients were pediatric but did not report a clinical specialty in pediatrics.

[24] In five cases, respondents were assigned to the pediatrics category on the basis of their open-ended responses provided when selecting "other" for their clinical specialty. For example, a respondent who entered "pediatric cardiology" was re-assigned to the categories of cardiology and pediatrics.

APPENDIX C: GENERAL DEVICE NEEDS FOR RARE DISEASE PATIENTS

General Device/Test Needs	Rare Diseases That Would Be Impacted	Diagnostic	Therapeutic
Ablation	Less invasive, more normal organ function preservation compared to surgery, fewer complications, better immune stimulation.		✓
A center that patients can be diagnosed	There needs to be a place where patients with rare disease can go to be evaluated. Then we would also have access to therapeutic trials.	✓	✓
Ability to culture/detect the abnormal cells of the disease if in circulation	LAM, Birt Hogg Dube.	✓	✓
Ability to diagnose or screen with high sensitivity and specificity	Genetic diseases and syndromes, autoimmune disorders, perhaps pancreatic and other cancers; thinking more broadly, dementias.	✓	✓
Accessibility to telemedicine for expert assessments	Virtually all rare diseases could benefit.	✓	✓
Advancements in radio-labelled antibodies to pinpoint disease	Malignancies which may be targeted.	✓	✓
An effective device to assist in gait	Any disorder requiring assistance with gait.	✓	✓
An effective device to assist in hand use	Any disorder in which hand use is limited, whether acquired or developmental.	✓	✓
Better marker for acute kidney injury (AKI)	Acute kidney injury (AKI), critically ill patients, conditions which require accurate GFR for drug dose.	✓	✓
Better measure of glomerular filtration rate (GFR)	Chronic kidney disease (CKD), acute kidney injury (AKI), oncological conditions which require accurate GFR for drug dose, critically ill patients.	✓	✓
Biomarkers that more closely mirror disease severity and response to therapy	All.	✓	✓
Biomarkers with diagnostic and prognostic value	Applicable to all.	✓	✓
Blood pressure and systemic blood flow control	Guillain-Barré, Dopamine beta-hydroxylase deficiency.	✓	✓
Blue-tooth capable health monitoring devices	Any rare disease in which patient health and therapeutic intervention needs to be monitored concurrently.	✓	✓
Communication	Rett syndrome.	✓	✓

General Device/Test Needs	Rare Diseases That Would Be Impacted	Diagnostic	Therapeutic
Communication devices for intellectually disabled children	Any neurodevelopmental genetic syndrome would be impacted. There are speech-generating augmentative communication devices but these still have significant inadequacies and are expensive and difficult to implement for first time use or single use (need to load child-specific features).	✓	✓
Databases of the disorders with an app that allows access for learning and sharing data/experiences—an aggregation of case reports and meta-analyses	Any one person or clinical team would know what is known in the experience of the disorder—both diagnostic and therapeutic. Too often, rare diseases are communicated in case reports or not at all. So, simple Internet access and means of reporting would be expected to create a more complete picture of the experience and not require subspecialists in the diagnosis and therapy of such individual[s]—especially in nonurban areas.	✓	✓
Detecting gene abnormalities for cystinosis	Nephropathic Cystinosis. Infantile Cystinosis. Adult onset Cystinosis.	✓	✓
Detecting gene abnormalities for PKD	Autosomal recessive PKD. Autosomal dominant PKD. Variations in both.	✓	✓
Detecting gene abnormalities for primary hyperoxaliuria	Type 1 and type 2 hyperoxalosis.	✓	✓
Device that can detect seizures during sleep/at night	Again, most affecting the brain.	✓	✓
Devices that are patient specific for the pediatric population	Range of respiratory, cardiovascular, musculoskeletal, and gastrointestinal conditions that require surgical reconstruction.		✓
Devices that can resorb and not require second surgery for the pediatric population	Range of respiratory, cardiovascular, musculoskeletal, and gastrointestinal conditions that require surgical reconstruction.		✓
Devices that can be 3D printed for patients	Range of respiratory, cardiovascular, musculoskeletal, and gastrointestinal conditions that require surgical reconstruction.		✓
Diagnosis is a start but ultimate goal should be effective treatment		✓	✓

General Device/Test Needs	Rare Diseases That Would Be Impacted	Diagnostic	Therapeutic
Diagnostic genetic testing—should be inexpensive		✓	✓
Diagnostic testing	All of them.	✓	✓
Diagnostic testing and collagen modification for Larsen's	Larsen's patients.	✓	✓
Drug screens	All.	✓	✓
Early and accurate diagnosis	tuberous sclerosis, lymphangioleiomyomatosis	✓	✓
Early and effective therapy	tuberous sclerosis, lymphangioleiomyomatosis	✓	✓
Easier ways to gain approval for devices for children once they are approved in adults	Many.	✓	✓
Effective therapies	All.	✓	✓
Fast and reliable	Almost all.	✓	✓
Flow cytometry	MRD.	✓	✓
Functional testing of known immunodeficient patients	Combined immunodeficiencies, other severe combined immunodeficiency disorders, metabolic disorders	✓	✓
Genetic testing panels for given phenotypes	Most	✓	✓
Genetic testing, particularly tests that yield information that could better phenotype/subtype children with a particular disorder	Pulmonary hypertension complicating bronchopulmonary dysplasia. Pulmonary hypertension complicating congenital diaphragmatic hernia.	✓	✓
Immunological techniques	Cancers.	✓	✓
Improved collaboration of institutions that treat these diseases (expanding PIDTC)	Therapeutic management of all immunodeficiencies.	✓	✓
Inexpensive	Almost all.	✓	✓
Inexpensive blood tests for diagnosis and monitoring	Many rare diseases.	✓	✓
Intrathecal delivery	MPS, GM.		✓
Less expensive treatments—rare diseases have a disproportionate share of medical burden due to cost	Bleeding disorders, immune deficiencies, metabolic diseases, porphyria.	✓	✓
Less invasive	Pancreatic cancer.	✓	✓
Lower cost	All.	✓	✓

General Device/Test Needs	Rare Diseases That Would Be Impacted	Diagnostic	Therapeutic
Metabolomics for disease subgrouping	Sarcoidosis. Idiopathic pulmonary fibrosis. Connective tissue diseases.	✓	✓
More individualized prognosis information	Progressive supranuclear palsy, multisystem atrophy, corticobasal syndrome, Huntington's disease, neurodegeneration with brain iron accumulation, dystonia, spinocerebellar ataxia.	✓	✓
More rapid access to caregivers that have an understanding of the disease	Probably all.	✓	✓
More specific	All.	✓	✓
Next generation sequencing	MRD.	✓	✓
Noninvasive and fast neuroimaging		✓	✓
Noninvasive markers for monitoring disease activity	All eosinophilic gastrointestinal diseases.	✓	✓
Noninvasive	Many.	✓	✓
Noninvasive	Mitochondrial.	✓	✓
Other alternative route of administration devices for medications, lab sampling	Arguably too many to count. Quality of life and ability to manage disease out of the healthcare setting would be enhanced.	✓	✓
Patient reported outcomes	All of them.	✓	✓
Reliable	Many.	✓	✓
Reliable diagnostic tests	All.	✓	✓
Reproducible	Mitochondrial.	✓	✓
See earlier responses	Huntington's disease.	✓	✓
Serum or non-tissue diagnosis of mitochondrial disease in children	Spectrum of mitochondrial disease which is often not diagnosed until late, and based on tissue specimen. Newborn or prenatal testing etc. can result in better counseling for these patients.	✓	✓
Serum test	LAM,TSC.	✓	✓
Should enable early diagnosis		✓	✓
Smaller delivery systems or alternative routes of device delivery for smaller patients	Numerous...too many to count.	✓	✓
Some of the infectious diseases		✓	✓
TERM strategies	Congenital heart diseases.	✓	✓

General Device/Test Needs	Rare Diseases That Would Be Impacted	Diagnostic	Therapeutic
Tests that allow home monitoring by patients of disease and treatment side effects	Many rare diseases.	✓	✓
Therapy tracker	All of them.	✓	✓
tools for a more rapid diagnosis	All.	✓	✓
Transcutaneous, non-invasive monitoring devices for disease activity	I am sure that such devices would have broad applications for all diseases and conditions.	✓	✓
Treatment for chronic graft-versus-host disease		✓	✓
Tumors of unknown primary	Identify better treatment regimens.	✓	✓
Unusual infections	Fungal infections, parasites, immunocompromised patients.	✓	✓
Vaccines for inherited cancer syndromes	The current (and life-saving) gene-specific management for inherited syndromes is routine high risk surveillance (typically starting quite young) with the aim at early detection and cure (surgical) or prophylactic surgery. Our patients, while grateful, feel this is “not the life.” Thus, vaccines or other preventatives for inherited cancer syndromes are much needed.	✓	✓
A device to control incontinence in older children and adults	Postsurgical Hirschprung’s disease and rectal pull-through procedures for IBD, for example. Children with spina bifida.		✓
Adaptive supports for motor/motility challenges	Neurodevelopmental disorders associated with motor delays and deficits.		✓
Airway devices	Many with craniofacial differences.		✓
Allow more flexible sizes	Left main CAD, HOCM.		✓
Alternating or direct current stimulation	HD, CF.		✓
Alternative to epicardial pacing leads for single ventricle physiology	Any patient with conduction abnormalities in the face of single ventricle physiology presents a challenge to conventional intravascular pacing leads. The current approach is to place leads on the surface of the heart where interventions have commonly caused significant scarring and poor access for appropriate electrical connection to the heart tissue. As survival with single ventricle physiology has improved, the difficulty of pacing has been a significant challenge.		✓
Alternatives to blood products	Blood production disorders.		✓

General Device/Test Needs	Rare Diseases That Would Be Impacted	Diagnostic	Therapeutic
Ambulation devices	Several with neuromuscular involvement.		✓
Approval of topical corticosteroids	EoE.		✓
Automated, live, and instant dietary assessments to tailor nutrition	All rare diseases which need a special diet to improve symptoms, delay progression, or cure...		✓
AV grafts for hemodialysis which last longer without complications	Children and adults on dialysis.		✓
Availability of devices that are possible but too expensive because of small numbers who need them	Hydrocephalus, idiopathic intracranial hypertension, syndromic craniosynostosis.		✓
Better targeting of therapies to alter disease pathogenesis or etiology	Almost all of them.		✓
Better understanding of whole-exome sequencing (WES) and other large-scale sequencing methods	Many; but specifically early infantile epileptic encephalopathies.		✓
Biocompatible implantable devices	Congenital and/or acquired cardiac disease.		✓
Biomarkers of treatment response	Multiple.		✓
Blood brain barrier transport system	Diseases that affect nervous system development and function.		✓
Brain machine interfaces	High quadriplegia, brain stem stroke (locked-in syndrome), advanced motor neuron disease (e.g., ALS).		✓
Brain stimulation devices	Unclear at this point.		✓
Brain-computer interface	ALS, Werdnig-Hoffmann disease (type I spinal muscular atrophy), others with loss of muscle/limb control.		✓
Cell-based genetic therapies that can restore normal organ function	Congenital or acquired cardiomyopathies.		✓
Cellular therapy/dialysis devices for metabolic disorders	Glycogen storage diseases, enzyme deficiencies.		✓
Cochlear implants for younger infants that adapt in size	Congenital deafness.		✓
Continuous glucose measurement with glucose infusion in kids with glycogen storage disease	Glycogen storage disease.		✓
Correction of diabetic Charcot foot deformity	Self-explanatory.		✓

General Device/Test Needs	Rare Diseases That Would Be Impacted	Diagnostic	Therapeutic
Cortical stimulators (either implanted or surface)	Rett syndrome.		✓
Covered stents for pediatric patients.	Any vascular abnormality where stenting might be required that might be associated with a high risk of vascular dissection/rupture.		✓
Customized treatment	Recurrent respiratory papillomatosis, acoustic neuroma, anaplastic thyroid cancer.		✓
Deep brain stimulators	Rett syndrome.		✓
Delivery of drugs	Mendelian diseases.		✓
Development of alternative medications	EoE.		✓
Devices for delivery of drugs across the blood brain barrier	Encephalitis.		✓
Devices for diseases that affect mostly children	Hydrocephalus, syndromic craniosynostosis.		✓
Devices for prenatal delivery of therapeutics	Smith Lemli Optiz syndrome.		✓
Devices that allow control of body functions by activation linked to EEG control	SMA, muscular dystrophies, congenital neuropathies.		✓
Devices that are responsive to physiological changes (i.e., responsive neurostimulation for epilepsy)	All that involve seizures.		✓
Devices that grow with a child; even cardiac valves that have the potential to expand with growing child so that they are not requiring repeated surgeries during their lifetime	Children with any form of incompetent (genetic or acquired) cardiac valve.		✓
Devices that grow with the child			✓
Devices to deliver drugs intrathecal	NNS infections, autoimmune disorders, spasticity, epilepsy.		✓
Devices to improve ambulation or prevent falls for children with refractory movement disorders	Genetic/metabolic/inflammatory causes of pediatric movement disorders.		✓
Devices to treat movement disorders	Genetic/metabolic/inflammatory causes of pediatric movement disorders.		✓
Drug delivery	Less systemic toxicity, higher doses to target region.		✓
Drug delivery	ALS, PLS.		✓

General Device/Test Needs	Rare Diseases That Would Be Impacted	Diagnostic	Therapeutic
Drug delivery devices that are controlled by feedback from physiologic sensors	Virtually every rare disease where a drug/dose relationship to the severity of disease is known.		✓
Drug delivery systems that sense either changes in biomarkers or changes in acute clinical manifestations (e.g., seizures, aggressive behavior)	Most rare diseases affecting the CNS.		✓
Drug delivery to area of interest	Central nervous system tumors. Glomerular diseases.		✓
Dytonia-full FDA approval	See previous.		✓
Early treatment of neurofibroma to prevent extensive growth	Neurofibromas.		✓
Easy to use treatment	Metabolic disorders in children.		✓
Effective long-lasting treatment	Lymphangiomyomatosis, congenital heart disease.		✓
Effective treatment	Metabolic disorders in children.		✓
Effective treatments	Most, I would hope. Different treatment for each.		✓
Endoscopic lung volume reduction	Possible LAM and Birt-Hogg-Dubé syndrome—not yet been evaluated.		✓
Enteral stents	Pancreas cancer, small bowel cancer, gastric cancer.		✓
Enzyme delivery system that would avoid need for weekly infusions	Mainly lysosomal storage diseases, but perhaps many other metabolic enzyme deficiencies.		✓
Enzyme replacement therapy	Many genetic diseases.		✓
Exchange groups for patients to discuss successful jury-rigged devices	Several hundred/thousand rare diseases.		✓
Exoskeleton	Many inherited neuromuscular disorders.		✓
Expandable implants	OI (Osteogenesis Imperfecta).		✓
Feeding devices	Several associated with GI dysmotility.		✓
Functional implantable prostheses for limb sparing surgery in bone sarcomas	Osteosarcoma, chondrosarcoma, synovial sarcoma, Ewing's sarcoma, rhabdomyosarcoma.		✓
Gene editing	Primary ciliary dyskinesia, cystic fibrosis.		✓
Gene modification to correct genetic defects in cellular function	Many diseases, such as sickle cell, thalassemias, enzyme defects, genetic susceptibility to diabetes, heart disease, cancer.		✓
Gene replacement	Very many.		✓

General Device/Test Needs	Rare Diseases That Would Be Impacted	Diagnostic	Therapeutic
Gene replacement therapy	All rare diseases.		✓
Gene therapy	Sickle cell disease, thalassemia, cystic fibrosis.		✓
Gene therapy	Single-gene disorders.		✓
Gene therapy	Any disease transmitted genetically.		✓
Gene therapy in stem cells	Disorders of lympho hematopoiesis due to single gene mutations.		✓
Gene transfer	Many genetic diseases.		✓
GI motility aids (i.e., a more generalized "gastric pacemaker")	All manner of GI inflammatory conditions, neuromuscular disease, CF, etc.		✓
Growing joint prosthesis for children	Any rare disease that causes early joint degenerative arthritis or deformity.		✓
Heart valves and other implants that might grow with a child	All pediatric congenital heart diseases.		✓
Home mechanical ventilation for children	TBI.		✓
Home testing/monitoring devices for clinically relevant analytes	Inborn errors of metabolism—UCD, MSUD, PKU, organic acidemias.		✓
Home treatment devices or biologics	Inborn errors of metabolism.		✓
Home treatment	Any disease		✓
Implantables that may grow with the individual or that can be tuned or modified without need of explanation	This would have broad applicability, particularly with management of pediatric patients but also potentially useful in adults.		✓
Implantable chemotherapy delivery devices for children	Rare forms of pediatric cancer.		✓
Implantable detoxification devise for specific proteins	Many.		✓
Implantable drug delivery devices	Most neurologic diseases if the drug delivery is intrathecal.		✓
Implantable drug delivery system	Many.		✓
Implantable pain medication dispenser	Any chronic condition causing pain.		✓
Implantable pumps to deliver drug	Urea cycle defects. Organic acidemias.		✓
Implanted device compatibility for MR	All pediatric diseases, most adult.		✓

General Device/Test Needs	Rare Diseases That Would Be Impacted	Diagnostic	Therapeutic
Implanted devices that can grow with the child	Heart disease in children is the easiest one to discuss. Valves or cardiac pacemakers need frequent replacing. CNS shunts have similar issues, so this type of device would also impact many rare diseases where hydrocephalus is a component.		✓
Implants that resist infection	Pumps for drug delivery (e.g., Baclofen pumps for spasticity).		✓
Improve cognitive function	Frontotemporal dementias, progressive supranuclear palsy, corticobasal syndrome, Huntington's disease, neurodegeneration with brain iron accumulation.		✓
Improve/expand use of intracranial devices	Refractory epilepsies, tumors, neurodegenerative diseases.		✓
Improved drug delivery devices that reduce systemic exposure/harm	Again, virtually all lung diseases would be better with lung-specific targeted therapy.		✓
Improved hearing aid	Many of these diseases also have hearing loss and will help with speech too.		✓
Improved oxygen delivery devices	All diseases that result in the need for supplemental oxygen.		✓
Improved oxygen delivery techniques	Any lung disorders that lead to hypoxemia—both rare and more common such as pulmonary fibrosis, connective tissue related diseases, etc.		✓
Improved portable O2 delivery devices and associated oximetric monitoring with activity	Those involving pulmonary disease and associated exertional hypoxemia.		✓
In younger children, an improved, expandable rod system for scoliosis surgery	Any disorder with progressive scoliosis requiring intervention before linear growth is largely complete.		✓
Intrathecal catheters for pediatric patients that accommodate growth	Sickle cell disease and pediatric cancers.		✓
Intraventricular delivery devices	Rett syndrome.		✓
IV access ports that don't get infected	Many metabolic disorders, GI disorders, cardiac disorders, cancers. This would have huge impact.		✓
Joint replacement implants for juvenile arthritis	Juvenile arthritis.		✓
Likely genetically based therapies	DYT1, THAP1, Lesch-Nyhan, PKAN Huntington's, RDP.		✓
Long gap esophageal atresia	Long gap esophageal atresia.		✓
Means for neurologic regeneration	Traumatic brain and nerve injuries.		✓

General Device/Test Needs	Rare Diseases That Would Be Impacted	Diagnostic	Therapeutic
Means of patient having and sharing complex organized medical health records	All—it would allow better dissemination to other health care providers about the details, relative contraindications, treatments, and risks of having the rare disease.		✓
Medical treatment for mucopolysaccharidosis	Those with the disease and their families.		✓
Medications that don't have to be delivered by the IV route (very hard for most people)	Porphyria, bleeding disorders, immune deficiencies, enzymopathies, metabolic disorders.		✓
Minimally invasive	Parkinson's, congenital heart disease.		✓
Minimally invasive/microdrug delivery systems	SOD.		✓
Mobility	Progressive supranuclear palsy, multisystem atrophy, corticobasal syndrome, Huntington's disease, neurodegeneration with brain iron accumulation, dystonia, spinocerebellar ataxia, ataxia telangiectasia.		✓
Modifiable implants	OI.		✓
Needle-free infusion	Many kids would benefit. Sptingleaf tried to develop a system that looked promising but failed as a company last year.		✓
New biologics	Rare rheum diseases with ILD; PAP.		✓
New therapeutic instruments	Fetal therapies for congenital heart surgery, ablation therapies for early cancers.		✓
Non-genetic methods to test for disease	Same as previous.		✓
Non-invasive ablation of tumor cells without chemo or radiation	Bone cancers (osteosarcoma, lymphoma).		✓
Non-invasive airway support for the home setting	All neuromuscular diseases and diseases that affect respiratory drive and ability.		✓
Non-invasive strategies to recover molecular function in monogenetic diseases	All disease caused by deleterious genetic variants.		✓
Non-pharmacologic pain-management device	Postsurgical treatment of chronic pain related to cancers.		✓
Novel CNS drug delivery devices	Spinal muscular atrophy in short term as well as potentially multiple disorders of CNS long term.		✓
Novel methods of drug delivery	Pancreatic cancer.		✓
Oral medications	Improve the ability of patients to take medications at home with a less invasive route.		✓

General Device/Test Needs	Rare Diseases That Would Be Impacted	Diagnostic	Therapeutic
Organ/tissue replacement	Peter's anomaly, congenital glaucoma.		✓
Pacemakers and defibrillators that accommodate pediatric patient grown	Pediatric patients with either congenital ion channelopathies (for example, Long QT syndrome), or congenital complete heart block requiring pacing.		✓
Paracorporeal lung device	Infants with congenital diaphragmatic hernia, genetic disorders of surfactant metabolism.		✓
Patient size-specific devices	Congenital and/or acquired cardiac disease.		✓
Patient specific shapes (for craniofacial or body dysmorphologies)	Several hundred/thousand rare diseases.		✓
Patient-specific sizing (neonates, pediatric, obese, ...)	Several hundred/thousand rare diseases.		✓
Pediatric devices for fracture fixation	All pediatric fractures of long bones.		✓
Pediatric implants that do not require anticoagulation or antiplatelet therapies	Congenital heart diseases after surgical repair or palliation.		✓
Pediatric pacing and acid devices	Pediatric arrhythmias.		✓
Pediatric-sized cardiac help devices that can be used to bridge to transplant	Especially the muscular dystrophies which impact heart function.		✓
Pediatric specific with small size and growth capabilities	Spine problems, fractures.		✓
Pediatric-sized cardiovascular devices	Thrombotic complications of pediatric chemotherapy, congenital and posttraumatic thrombotic disorders.		✓
Pharmacological agent that is curative	Many—LAM, Birt-Hogg-Dubé, pulmonary alveolar proteinosis		✓
Port for stem cell supplement	Too many to mention. Leukemia, inborn enzyme deficiency, etc.		✓
Practical growth sparing instrumentation for spinal kyphosis	Kyphoscoliosis in the young child.		✓
Predictive biomarker tests for disease progression	X-linked adrenoleukodystrophy, inborn errors of metabolism.		✓
Prolonged release of therapeutic enzymes or drugs	Cancer or hereditary enzyme deficiency.		✓
Promoters of neurologic repair	Neurodegenerative diseases. Neurologic injuries.		✓
Rapid measurement of specific toxic metabolites	Most inborn errors of metabolisms.		✓
Refinement of deep brain stimulation	Dystonia, Huntington's.		✓

General Device/Test Needs	Rare Diseases That Would Be Impacted	Diagnostic	Therapeutic
Rehydrate spinal disc	Disc replacement.		✓
Replacement enzyme therapies	Rare disorders of metabolism.		✓
Replacement of missing genetic product			✓
Restoration of function (sensory, motor)	NF2.		✓
Safe long-term intravenous access	Any disease that was sufficiently volatile to require many admissions or treatments for intravenous care over a lifetime.		✓
Secure (e.g.) pin head-holders for intraoperative MRI image guidance for young children	Brain tumors, vascular lesions, intractable epilepsy.		✓
Site-specific drug delivery	Brain tumors, such as non-operable brain stem gliomas, which are currently incurable.		✓
Skeletal and other implants that can be adjusted as the child grows	Pectus excavatum, scoliosis, bony growth abnormalities.		✓
Skeletal dysplasia	Lethal skeletal dysplasia, perinatal death, short stature, bone fractures, hypophosphatasia congenita.		✓
Small molecule chaperone or read-through compound delivery system	Many genetic disorders.		✓
Smaller, more efficient oxygen delivery systems	All lung diseases causing hypoxia.		✓
Steady delivery of missing drug (agent) that would correct deficiency recognized	Lipoatrophic DM, likely make persons more tolerable and less complicated. Earlier diagnosis of MODY.		✓
Stem cells	Primary ciliary dyskinesia, cystic fibrosis.		✓
Stents and other "dissolving" vascular devices of appropriate size for pediatric patients (pulmonary arteries coarctation, etc.)	Tetralogy of Fallot and other diseases associated with pulmonary artery stenosis. Stents are also applicable for vascular compromise in other structures as consequence of abnormal development, sequelae of other diseases, or scarring from other interventions.		✓
Suprachoroid stents	See above.		✓
Tests that can predict response to anticonvulsants	Most effecting the brain.		✓
Tissue engineered heart valve	Congenital valve disease of many forms.		✓
Tissue engineered heart valve conduit	Pulmonary atresia.		✓
Tools to document compliance with taking drugs.	Erythropoietic protoporphyria. Porphyria cutanea tarda.		✓
Tourette's syndrome-HDE	Tourette's.		✓

General Device/Test Needs	Rare Diseases That Would Be Impacted	Diagnostic	Therapeutic
Transcranial magnetic stimulation	Huntington's disease, cystic fibrosis.		✓
Ultrasonic mesh-type nebulizers for delivering medications to the respiratory tract.	Autoimmune PAP.		✓
Use of 3D printing technology to enhance patient-prosthesis matching			✓
Use of 3D printing to make patient-specific implants based upon imaging studies	Cardiac disease, small bowel transplantation, joint replacement.		✓
24-hour intraocular eye pressure monitoring	All types of pediatric and adult glaucoma, both rare and common.	✓	
A cheaper, easier genomics testing platform to diagnose rare genetic disorders	Many rare genetic disorders that may cost thousands of dollars to diagnose and take a long time. A faster, easier, and more accurate way of doing this.	✓	
A general test for diagnosing Birt-Hogg-Dubé syndrome	Birt-Hogg-Dubé syndrome.	✓	
A general test for diagnosing tuberous sclerosis (TSC)	TSC-Lymphangiomatosis (LAM).	✓	
A widely available, rapid test for urinary PBG with very fast turnaround time	Porphyrias. Many other disorders that may present in similar ways.	✓	
Accurate diagnosis	Sarcoidosis.	✓	
ADAMTS13 concentrate	TTP (acquired and congenital).	✓	
Additional specific genetic tests	Many of the pediatric disorders, including isolated dystonia and secondary dystonias.	✓	
Affordable genetic testing.	Nearly all.	✓	
Alternate tracers for MR and CT PET	Storage diseases, myeloma, etc.	✓	
Available and low-cost test	Pancreatic cancer, multiple myeloma and other malignancies, genetic disorders, dementias, infectious diseases, HIV, etc.	✓	
Better diagnostic testing	Cancers, such as pancreatic.	✓	
Better diagnostic testing	More rare neurologic entities.	✓	
Better endoscopic devises for hepatic and pancreatic screening in children	Pancreatitis in childhood, biliary disease in childhood.	✓	
Better genetic testing	Nearly all genetic disorders with a multiple genes.	✓	
Better genetic testing	Combined immunodeficiencies would be the most directly affected diseases within my realm.	✓	

General Device/Test Needs	Rare Diseases That Would Be Impacted	Diagnostic	Therapeutic
Better genetic testing	Almost all of them.	✓	
Better genetic tests	Familial hypercholesterolemia, HOCM, HIT.	✓	
Better imaging	Most!	✓	
Better imaging techniques for little patients—pediatric age	Uterovaginal anomalies.	✓	
Better symptom specific genetic screening tests	Prolonged chronic diarrheal syndromes in children, hepatic fibrotic diseases and pancreatitis in children, incontinence secondary to surgical intervention in diseases, such as Hirschprung's disease, as well as in children with spina bifida, etc.	✓	
Biochemical enzyme analysis methods	Many inherited metabolic diseases.	✓	
Biochemical tests	LCAT deficiency.	✓	
Biomarker testing	All diseases without markers for disease progression and therapeutic outcomes.	✓	
Biomarkers	Several.	✓	
Biomarkers of epilepsy	Post traumatic epilepsy, other epilepsies with acquired causes.	✓	
Biomarkers of SUDEP	SUDEP.	✓	
Biopsy	Better diagnoses, quicker diagnoses, less invasive diagnoses, less painful.	✓	
Biopsy	Many rare diseases would be impacted.	✓	
Blood biomarker	bvFTD. CBD. CTE.	✓	
Blood test	Many rare diseases would be impacted.	✓	
Blood testing for diagnostic purposes	All, including inborn errors of metabolism, acquired syndromes, genetic illnesses like Long QT.	✓	
Blood tests/tumor-specific markers	Pancreas cancer, esophageal cancer.	✓	
Body imaging that does not require intravenous contrast agents	All oncologic and cardiovascular diseases.	✓	
Breath testing	LAM, LCH, alpha-1 antitrypsin deficiency and probably many others.	✓	

General Device/Test Needs	Rare Diseases That Would Be Impacted	Diagnostic	Therapeutic
Broader availability of genetic tests	Birt-Hogg-Dubé disease. Tuberous sclerosis. Familial pulmonary fibrosis.	✓	
Cell-based assay (patient sera on target cells, i.e., cross match)	Any rare renal disease caused by circulating factors, such as FSGS.	✓	
Cerebrospinal fluid biomarker	bvFTD. CBD. CTE.	✓	
Cheap convenient genetic tests that can be done onsite	Any genetic diseases.	✓	
Cheaper genetic tests and the mechanism for understanding the functional relationships.	All rare diseases as we identify how genetic variability translates into protein function. It would also improve the sensitivity for treating conditions that have variable phenotypes, so that patients with moderate or mild symptoms are not swept under the rug because their symptoms don't "perfectly fit" into the diagnostic category, especially x-linked recessive disease in women.	✓	
Chemotherapy metabolism panel	Liver metabolism of chemotherapy drugs.	✓	
Congenital immunodeficiency panel	Immunodeficiencies.	✓	
Detection of genetic diseases at clinic	All genetic diseases.	✓	
Development of indicators for monitoring condition status		✓	
Device that can collect a small amount of DNA for detection of a somatic mutation without need for a skin biopsy	An increasing number of syndromes now being recognized to be somatic and a much greater number suspected to be.	✓	
Diagnosis of Hirschsprung**'s** disease	Determination of transition zone and where "good bowel begins" in children with congenital HD.	✓	
Diagnosis of indeterminate colitis (Crohn's vs. ulcerative)	Would better define type of operation.	✓	
Diagnostic blood tests	All.	✓	
Diagnostic tests (blood tests) for the various rare diseases		✓	
Disease-specific biological marker assays	Many; but the two diseases I've previously listed are important examples.	✓	
Disease-specific genetic testing	Many; but the two I've previously listed are important examples.	✓	

General Device/Test Needs	Rare Diseases That Would Be Impacted	Diagnostic	Therapeutic
DNA analysis (genetic test)	Alveolar microlithiasis. Tuberous sclerosis complex.	✓	
Earlier diagnostic testing	Pancreatic cancer.	✓	
Early diagnosis		✓	
Early diagnosis	Metabolic disorders in children.	✓	
Early diagnosis of the 90% of autism that is not genetic	Nongenetic autism (autism spectrum disorders).	✓	
Effective ways to target enzymes for specific tissues that are hard to access by current techniques	Lysosomal storage diseases. Most current therapies do not get adequate enzyme into affected tissues.	✓	
Evaluating functioning in non-verbal/motor impaired individuals	Rett syndrome	✓	
Exome sequencing that is readily accessible	Most of them.	✓	
Fast and economical genetic tests to confirm the diagnosis	Children with inborn errors of metabolism and rare genetic syndromes.	✓	
FDA approval of devices	Primary ciliary dyskinesia.	✓	
Flow cytometry	MRD.	✓	
Functional MRI testing	Primarily neurological versus psychiatric diseases.	✓	
Functional tests for confirming mutation pathogenicity	All rare genetic diseases could be impacted if one or more general tests could be developed to determine the pathogenicity of mutations.	✓	
Gadolinium-free MRI with contrast	Benign brain tumors needing extended surveillance.	✓	
Gene mutational analysis	AA, SCID, HLH.	✓	
Gene sequencing with high throughput and turn around to test for multiple conditions		✓	
Genetic diagnosis		✓	
Genetic modification techniques	Various childhood genetic diseases as hurlers, dwarfism, sickle cell, etc.	✓	
Genetic screening for all podocytopathies	Nephrotic syndrome.	✓	
Genetic testing	Some retinal diseases.	✓	
Genetic testing		✓	
Genetic testing	Potential early detection and treatment, possible prevention.	✓	

General Device/Test Needs	Rare Diseases That Would Be Impacted	Diagnostic	Therapeutic
Genetic testing	Recurrent respiratory papillomatosis, anaplastic thyroid cancer, acoustic neuroma.	✓	
Genetic testing	Darier's disease; epidermolysis bullosa; ichthyoses (various); severe, chronic hand eczema.	✓	
Genetic testing	Better diagnosis and greater understanding of rare diseases—and possibly also common ones.	✓	
Genetic testing	Inherited neurological disorders.	✓	
Genetic testing	All.	✓	
Genetic testing	1. Metabolic diseases that do not have current therapy. 2. Diseases where it unclear why the progression has not followed known course based on experience. 3. Where disease is multifactorial: for example, Trisomy 21 + pulmonary hypertension + chylothorax + methylmalonic acidemia.	✓	
Genetic testing	ALS, PLS.	✓	
Genetic testing	Nephrotic syndromes in general	✓	
Genetic testing for genetic testing preconception	Any disease that is genetically transmitted.	✓	
Genetic testing more generally understood	MODY, lipoatrophic DM.	✓	
Genetic testing panels capable of diagnosing organ specific disease groups	The diagnostic delay for most genetic lung diseases remains very long. An inexpensive panel would save time, money, and patient lives.	✓	
Genetic testing panels in childhood to diagnose adult onset diseases	Alpha-1 antitrypsin deficiency needs to be tested for in childhood to avoid cigarette smoking, dust, and fumes in adolescence.	✓	
Genetic testing post birth	Huntington's and any other disease which would develop at a later age.	✓	
Genetic tests	LCAT deficiency, hypobetalipoproteinemia, Tangier disease, lipodystrophy, LPL deficiency, hepatic lipase deficiency, abetalipoproteinemia.	✓	
Good screening programs for certain diseases, especially colon and pancreatic cancer	Colon and pancreatic cancers.	✓	
Hemodynamic monitoring devices	Septic shock. Cardiac arrest.	✓	
High-resolution imaging	All congenital heart diseases, both rare and common cancers.	✓	

General Device/Test Needs	Rare Diseases That Would Be Impacted	Diagnostic	Therapeutic
Home monitoring devices for vitals and key metabolites	Cardiac, cancer, metabolic disorders of all kinds.	✓	
Home testing devices	Inborn errors of metabolism.	✓	
Home/self-monitoring of blood or saliva for disease specific abnormal metabolites and medication levels	A variety of inborn errors of metabolism requiring special diets or medications.	✓	
Image technology	LAM, TSC.	✓	
Imaging platform to diagnose concussions	Sport-related head injury.	✓	
Imaging platform to predict degenerative brain disease	Alzheimer's, chronic traumatic encephalopathy.	✓	
Imaging tests for rare cardiac anomalies	Unicuspid unicommisural aortic valve stenosis.	✓	
Imaging tests without radiation risks in diagnosing and monitoring disease course	Many diseases affecting various organs, especially those that currently require the use of ionizing radiation.	✓	
Improved diagnostic instruments		✓	
Improved genetic testing for channelopathies	Short QT syndrome, catecholaminergic PMVT, Brugada syndrome, Long and Short QT syndrome.	✓	
Improved genetic testing for the presence of rare diseases	Hirschsprung's disease, Ehlers-Danlos syndrome type 3, cyclin neutropenia.	✓	
Improved MRI technology	Brain tumors, head injury, management of elevated intracranial pressure.	✓	
Improved noninvasive diagnostics	Multiple	✓	
Improved testing for genetic diseases; more sensitive and more rapid tests	An array of congenitally acquired genetic diseases.	✓	
Improved tests to differentiate among rare movement disorders	Progressive supranuclear palsy, dementia with Lewy bodies, multisystem atrophy, corticobasilar degeneration.	✓	
In office genetic testing	Aniridia, corneal dystrophies.	✓	
Inexpensive genetic testing	Many. You know the list.	✓	
Less expensive tests	All genetic testing.	✓	
Less invasive diagnostic test		✓	
Low radiation imaging for repeated testing	Lymphangioleiomyomatosis. Birt-Hogg-Dubé disease. Alveolar proteinosis. Sarcoidosis.	✓	

General Device/Test Needs	Rare Diseases That Would Be Impacted	Diagnostic	Therapeutic
Low-cost genetic testing	Ability to determine diagnosis, appropriate therapies, and prognosis. Ability to advance knowledge of genetic kidney diseases.	✓	
Lower need for blood volume; 5cc is a lot of blood for a newborn	All genetic testing.	✓	
Lung biopsy	All rare lung diseases requiring biopsy specimens being obtained.	✓	
Minimally invasive brain pressure monitoring	TBI.	✓	
Molecular tests for the confirmation of diagnosis	Congenital marrow failure syndrome. Metabolic disorders. Immunological disorders.	✓	
More affordable and easily accessible genetic testing for cardiac ion channelopathies	All the genetic ion channelopathies, such as Long QT syndrome, arrhythmogenic right ventricular dysplasia, Brugada syndrome, and many others. Even though some of these diseases don't generally cause arrhythmias until adulthood, often genetic testing of children whose parents have a known or suspected genetic ion channelopathy is recommended but difficult for patients to get.	✓	
More and better genetic tests to help diagnosis	Dystonia.	✓	
More sensitive and specific genetic profiling	Too numerous to count (i.e., a significant percentage).	✓	
More specific and sensitive tests for diagnosis	Almost all of them.	✓	
More specific diagnostic criteria	Dystonia. Cervical dystonia. PSP.	✓	
More specific markers that differentiate pancreatic cancers from others	Pancreatic carcinoma, biliary carcinoma, hepatocellular carcinoma.	✓	
NBS screening devices	CTX, sitosterolemia, SLOS, MKD, and likely all rare diseases that do not currently qualify for NBS because here is no cure.	✓	
Neurologic monitoring devices	Seizures. Encephalopathy. Intracranial hypertension.	✓	
Neurological imaging modality	bvFTD. CBD. CTE.	✓	

General Device/Test Needs	Rare Diseases That Would Be Impacted	Diagnostic	Therapeutic
Newborn screening test for all genetic diseases	Metabolic diseases, immune deficiency diseases, congenital blood disorders.	✓	
Next generation sequencing	MRD.	✓	
Next generation sequencing for rare diseases	Novel mutations predisposing to malignancies.	✓	
Non-invasive cellular and genetic testing	Bone cancers.	✓	
Non-invasive diagnostic tests	Neurodevelopmental disorders.	✓	
Non-invasive diagnostic tools	Eosinophilic Esophagitis (EoE).	✓	
Non-invasive maternal serum testing for rare diseases in the fetus	Same as noted above for the fetus—ease of access to detection; precision of diagnosis; no direct risk to the fetus.	✓	
Non-invasive measures of organ function	All rare diseases with chronic progressive disease if noninvasive measures capture chronic activation of fibrosis and or inflammation	✓	
Non-invasive methods to examine the retina and optic nerve (pertinent in many diseases)	Rare diseases affecting the central nervous system may potentially be monitored in children through non-invasive measurements of swelling and atrophy in retinal and optic nerve head tissue.	✓	
Non-invasive serum/urine biomarkers to establish diagnosis	Pulmonary Langerhans cell histiocytosis. Lymphangioleiomyomatosis. Sjogren syndrome.	✓	
Noninvasive testing (hair, saliva, etc.)	Numerous.	✓	
Non-invasive tests: spit, stool, pee, nail trimmings	Pancreatic CA.	✓	
Objective markers of behavioral syndromes for genetic disorders in children	Any neurodevelopmental syndrome associated with behavioral disorders.	✓	
Onsite genetic testing capabilities	Many associated with congenital heart disease and arrhythmias.	✓	
Panels with reflex testing logic for genetic diseases	Genetic diseases.	✓	
Pathogen discovery for encephalitis in immunocompromised patients	Encephalitis of unknown origin.	✓	
PET MRI	It would depend on the Nuclear Medicine Agents.	✓	
Photoreceptor imaging		✓	
Point of care diagnostic testing	All with genetic basis.	✓	

General Device/Test Needs	Rare Diseases That Would Be Impacted	Diagnostic	Therapeutic
Point of care genetic testing	LAM. Langerhans cell histiocytosis. Burt Hogg Dubé.	✓	
Postnatal diagnosis of metabolic disorders	Early diagnosis of muscular dystrophy, maple syrup disease, etc., especially where early intervention may have long-term benefit.	✓	
Potentially panel of modifier genes to help determine prognosis/risk	Potentially most.	✓	
Prenatal diagnostic tests for fetal abnormalities or inherited disorders	Any genetic events such as nondisjunction, inherited disorders, such as lipid storage disorders, etc.	✓	
Pre-natal gene testing for major congenital heart lesions	Spectrum of major congenital heart disease anomalies so better pre-natal diagnosis can be made, putting children at less risk after birth.	✓	
Pre-pregnancy genetic testing		✓	
Pre-symptoms determination of the severity of SCD	Sickle cell disease.	✓	
Quick (same-day) differential diagnosis specific DNA testing	Relatively rare causes of growth failure (e.g., GH receptor deficiency; IGF-I receptor mutation, bone dysplasia's), developmental delay, rickets.	✓	
Quick gene sequencing	POLG and other mitochondrial disorders in order to make drug requests.	✓	
Quick point of care test alveolar lavage in patients with ground glass infiltrates on CXR	Differential of ground glass on chest CT, includes pulmonary alveolar proteinosis, pneumocystis, alveolar hemorrhage, and others.	✓	
Radiation-free imaging modalities that don't require prolonged acquisition times	Nearly every rare disease that required cross-sectional imaging.	✓	
Rapid diagnosis	All.	✓	
Rapid diagnosis of infectious diseases (PCR based—get results in 1–4 hours)	TB.	✓	
Rapid genetic testing	Dravet syndrome, other rare genetic disorders.	✓	
Rapid turnaround genetic testing	Nearly all.	✓	
Rapid, accurate diagnostic tests	All of them.	✓	

General Device/Test Needs	Rare Diseases That Would Be Impacted	Diagnostic	Therapeutic
Real-time monitoring of intracranial shunts	Hydrocephalus. Traumatic brain injury.	✓	
Remote monitoring	Any disease.	✓	
Remote monitoring of biological signals with Web-based transmission (e.g., for heart rate, BP, sleep)	Spells of cardiovascular or central nervous system origin.	✓	
Respiratory monitoring devices	Acute respiratory failure. Chronic respiratory failure.	✓	
Retinal imaging	Retinal and choroidal diseases.	✓	
Routine whole exome sequencing for all	Many.	✓	
Screening lab test—metabolomics	Primary immune deficiency. Metabolic disorders.	✓	
Screening tests for pediatric DVT	Congenital thrombophilia.	✓	
Sensitive and specific	Mitochondrial.	✓	
Serum biomarkers for early diagnosis	Genetic predispositions to cancer.	✓	
Simple biomarker-based diagnostic tests.	Childhood rare lung diseases—virtually all.	✓	
Single test (DNA) that is inexpensive and covers all conditions (whole genome)	Most of the conditions that I see.	✓	
Small volume blood or tissue analysis (genetic and otherwise)	My perspective is the fetus, so beyond CF, it could include any number of uncommon genetic disorders, such as bone disorders, muscle disorders, etc.	✓	
Specific biomarkers	Especially cancers.	✓	
Specific blood test to diagnose diffuse skeletal hyperostosis	Diffuse skeletal hyperostosis, Ankylosing spondylitis, seronegative spondyloarthropathies.	✓	
Specific Blood test to diagnose reactive arthritis	Reactive arthritis, spondyloarthritis due to psoriasis, Ankylosing spondylitis.	✓	
Specific blood test to diagnose seronegative rheumatoid arthritis	Seronegative rheumatoid arthritis. Other seronegative arthritides, such as psoriatic and reactive arthritis.	✓	
Specific CSF and blood testing	Specific diagnosis allowing specific prescription; avoid missed diagnosis.	✓	

General Device/Test Needs	Rare Diseases That Would Be Impacted	Diagnostic	Therapeutic
Specific genetic testing	Degenerative spinal cord disease, spinal cord atrophy, complex movement disorders. Tourette's syndrome, behavior disorders in children, hysterical disorders, psychiatric diseases in children and adolescents.	✓	
Specific tests for diagnosis	Many.	✓	
Specificity of disease diagnosis	The previous question two pages back made no sense in terms of listing specific diseases. And, thus, these subsequent questions have no meaning.	✓	
Symptomatic biomarkers from common tests: EEG and other electrodiagnostics, such as AEP or VEP	Almost all pediatric rare genetic/metabolic diseases that are impacted by epilepsy and are associated with communication impairment.	✓	
Test to follow disease progression	All.	✓	
Testing other media than blood or biopsy	Pancreatic cancer, other cancers, immune diseases.	✓	
Testing without drawing blood	Any disease.	✓	
Tests for autoimmune disorders of the nervous system	Autoimmune encephalitis.	✓	
Tests that predict response to therapy	Any rare disease with variability in response to treatment or resistance to treatment.	✓	
Tumor genetic tests that predict prognosis	Triple negative breast cancer, any rare tumor, any rare disease with variable outcomes and penetrance in a population.	✓	
Vision testing		✓	
Ways to link genetic markers and imaging characteristics	Any rare malignancy.	✓	
Whole body MRI	Multiple myeloma, storage diseases.	✓	
Whole exome sequencing	Improved accuracy of diagnostics across all rare diseases.	✓	
Whole genome sequencing	All diseases with a genetic predisposition: -intellectual disability and autism syndromes, -cancer predisposition syndromes, -disorders that affect body growth.	✓	
Whole genome tests that are affordable and interpretable	Many genetic diseases.	✓	
Whole genomic sequencing of the patients at risk	Many diseases, but in my practice, marrow failure syndromes, metabolic disorders, immune deficiency diseases.	✓	

General Device/Test Needs	Rare Diseases That Would Be Impacted	Diagnostic	Therapeutic
Wider availability of whole-exome sequencing panels	Virtually all rare diseases would benefit.	✓	
X-linked Stapes Gusher syndrome	Degree of inner ear malformation.	✓	
Applicable to pediatric populations			
Churge Strauss syndrome	N/A.		
Drug development	Pancreatic cancer, cystic fibrosis.		
Etiology research for limb deficiencies	Limb deficiencies.		
Identifying variables which predict condition exacerbation			
Inexpensive	All.		
Knowledge of the genetic or environmental causes of rare diseases (including POI and vaginal septa)	POI and uterovaginal anomalies.		
Recognition of needs for psychological support for these kids (and parents)	POI and uterovaginal anomalies.		
Sickle cell disease	Complications of sickle cell disease—acute chest syndrome, bone and joint problems, cerebrovascular disease, pregnancy complications, pulmonary hypertension, need for transfusions.		
Sustainable pricing of devices	All.		
Synergy between FDA approval indication, guideline-based clinical use, and insurance coverage	All.		

APPENDIX D: RARE DISEASES SPECIFIED BY RESPONDENTS

Rare Diseases Mentioned
3rd-degree burns
Acanthamoeba keratitis
Achalasia
Acoustic neuroma
Active tuberculosis developing from latent infection
Acute cardiopulmonary failure in children (necessitating mechanical support like ECMO/VAD/etc.)
Acute lymphoblastic leukemia
Acute Porphyrias
Acute renal failure in children
Adrenal cortical carcinoma is an example
Adrenoleukodystrophies
Adult-onset Tay-Sachs disease
Airway support in children (dissolving stents for the trachea)
Alagille syndrome
Alpha 1 anti trypsin
Alport
ALS
Alternating hemiplegia of childhood
Alternative supporting testing for immune deficiencies is dispersed across the USA and not easily available
Amino acid disorders
AML/MDS
Amyloidosis
Anaplastic thyroid cancer
ANCA associated vasculitis
Aniridia
Anterior chest wall deficiency syndromes
ARPKD
Ataxia
Atrial septal defect
Atypical hemolytic uremic syndrome
Auditory neuropathy spectrum disorder
Autoimmune disorders of the CNS
Autoimmune encephalitis, e.g., anti-NMDAR-Ab
Auto-immune myositis
Avascular necrosis

Rare Diseases Mentioned
Axenfeld-Rieger syndrome
Bartholin gland carcinoma
Basal cell nevus syndrome
Batten disease—all forms
Best disease
Biliary atresia
Biodegradable scaffolds for congenital heart disease patients
Birt-Hogg-Dubé
Bone marrow failure syndromes
Bone sarcomas
Brainstem tumors (DIPG)
Bronchiectasis
Bronchiolitis obliterans syndrome
C3 Glomerulopathy
Cadasil
Carcinoid liver mets
Cardiac sarcoid
Carniofacial abnormalities
Carnitine-associated disorders
Catecholaminergic polymorphic VT
CDKL5 disorder
Central apnea in newborns
Ceroid lipofuscinosis
Cervical dystonia
CF
Charcot-Marie-Tooth disease
Childhood interstitial lung diseases
Childhood nephrotic syndrome
Childhood neuro disease like stroke and MS
Cholangiocarcinoma
Chronic exertional compartment syndrome
Chronic granulomatous disease
Chronic hypersensitivity pneumonitis
Chronic inflammatory demyelinating polyneuropathy
Chronic intestinal pseudoobstruction
Chronic myelogenous leukemia

Rare Diseases Mentioned
Chronic retinal detachment
Chronic traumatic encephalopathy
Combined immunodeficiencies
Cone dystrophy
Congenital neutrophil disorders
Congenital cardiac valve disease
Congenital diaphragmatic hernia
Congenital dilated cardiomyopathy
Congenital disorders of glycosylation
Congenital erythropoietic porphyria
Congenital glaucoma
Congenital heart disease
Congenital hydrocephalus
Congenital limb deficiencies, tibial and fibular hemimelia
Congenital micrognathia with airway obstruction
Congenital peripheral pulmonary artery stenosis
Congenital platelet disorders
Connective Tissue Disease
Corneal dystrophies
Corneal ectasia (post-refractive surgery, keratoconus, pellucid marginal degeneration)
Corneal stormal and anterior basement membrane dystrophies
Cornelia de Lange
Corticobasal degeneration
Cowden syndrome
Craniosynostosis
Cystic lung diseases
Cystinosis
Dent disease
Desmoid
Device for closure of preemie PDA
Diagnosis of myocarditis in children
Diagnostic testing for cholestatic liver disease in infants
Diagnostic tests for aortitis
Dravet syndrome
Duchenne muscular dystrophy
Duodenal atresia

Rare Diseases Mentioned
Dupuytren's contracture
DVT/PE in children
Dyskeratosis congenita
Dystonia
Early accurate intrauterine diagnosis of congenital heart disease and treatment
Early onset scoliosis
EB
Ebola and other viral hemorrhagic diseases
Ebstein’s anomaly
Ehlers-Danlos
Endovascular flow diverters for intracranial use
Eosinophilic colitis
Eosinophilic esophagitis
Eosinophilic gastritis
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)
ERT that crossed blood brain barriers
Erythropoietic protoporphyria
Esophageal adenocarcinoma
Esophageal atresia
Ewing’s sarcoma
Extreme microcephaly
Fabry disease
Facioscapulohumeral muscular dystrophy
Failing and dysfunctional single ventricle physiology
Familial exudative vitreoretinopathy
Familial hypercholesterolemia
Familial interstitial pneumonia
Familial LCAT deficiency
Familial Mediterranean Fever
Fatal diseases in infancy with mutated protein product
Fatty acid oxidation disorders
Fibrosing mediastinitis
Focal dystonia
Focal segmental glomerulonephritis
For a number of uncommon diseases, apheresis is the treatment of choice; getting new apheresis machines approved for all the indications has been very slow
FOXG1 disorder

Rare Diseases Mentioned
Gangliosidosis
Gastroparesis
Gastroschisis
Gaucher
Generalized dystonia
Genetic causes of aortic dissection and aneurysm
Genetic cholestasis syndromes
Genetic epilepsy syndromes
Genetic glomerulopathies
Genetic neurological disorders
Genetic testing for many immune deficiencies is not available except through WES which many insurance companies will not pay for
Genetic testing for rare abnormalities like polycystic kidney disease
Genetic testing identification
Giant cell arteritis
Glioblastoma multiforme
Glutaric aciduria
Graft-versus-host disease
Granular corneal dystrophy
Granulomatosis with polyangiitis—tests to assess disease activity
Gyrate atrophy
Heart failure with preserved ejection fraction
Hemophilia
Heparin-induced thrombocytopenia
Hereditary angioedema
Hereditary hemorrhagic telangiectasias
Hereditary pancreatitis
Hereditary spastic paraplegia
Hereditary retinopathies
Heritable pulmonary arterial hypertension
Hermansky-Pudlak syndrome
Heterotopic ossification of wounds
Hidradenitis suppurativa
HLH
Huntington’s disease
Hyperammonemia
Hypersensitivity pneumonitis

Rare Diseases Mentioned
Hypertrophic Obstructive Cardiomyopathy
Hypoplastic left heart syndrome
IBM
Ichthyosis
Idic 15
Idiopathic AVN of the hip
Idiopathic bronchiectasis
Idiopathic intracranial hypertension
Idiopathic pulmonary fibrosis
Idiopathic retroperitoneal fibrosis
IgA nephritis
Immunotactoid glomerulonephritis
Imperforate anus
Implantable artificial organs
Implantable pediatric transcatheter heart valve technology
Inborn errors of metabolism
Infantile epileptic encephalopathies
Infantile spasms
Inflammatory myositis
Inherited ataxias
Inherited retinal dystrophies
Internal carotid artery aneurysms warranting parent vessel sacrifice
Internal carotid artery dissection with associated symptomatic stenosis
Interstitial lung disease
Intraocular lymphoma
Invasive mycosis
Irregular corneal astigmatism
Isolated, idiopathic dystonia
Jarcho-levin
Jeune
Kawasaki disease
Keratoconus
Keratoglobus
Kleine-Levin syndrome
Krabbe disease
LAM

Rare Diseases Mentioned
Laminin deficiency
Landau-Kleffner Syndrome
Langerhans cell histiocytosis
Large congenital nevus
Large thermal burns 60% TBSA
Larsen's syndrome
Laryngeal dystonia
Lattice corneal dystrophy
Leber congenital amaurosis and other rare optic neuropathies
Leigh disease
Lennox-Gastaut syndrome
Lesch-Nyhan disease
Leucoencephalopathies
Leukodystrophies with the exception of adrenoleukodystrophies
Limb girdle muscular dystrophy
Limb ischemia without surgical or percutaneous options
Lipoatrophic diabetes
Lipodystrophy
Lipomyelomeningocele
Lissencephaly
:ong QT syndrome
Low-grade chondrosarcoma
Lung failure in newborn and children
Lymphangiomatosis
Lyosomal storage disease
Macular corneal dystrophy
Macular telangiectasia
Mal de débarquement syndrome
Malignant hyperthermia
Malignant migrating partial seizures of infancy
Many pediatric cancers
Many tropical infections (e.g., loa loa)
Maple syrup urine disease
Marfans syndrome aneurysms
Mast cell disease
Mcphelan-dermott

Rare Diseases Mentioned
MECP2 duplication disorder
Medulary thyroid cancer
Melanoma
MERS
Mesenteric venous thrombosis
Metabolic disorders
Microscopic polyangiitis-tests to assess disease activity
Minimal change disease
Minimal residue disease (MRD)
Mitochondrial disease
Moderate and severe pediatric traumatic brain injury
MODY
More transcatheter valve options for congenital patients (smaller sizes)
Mowat-Wilson syndrome
MPS
Mucus membrane pemphigoid
Muir-Torre
Multi-focal lymphangioendotheliomatosis
Multiple congenital anomaly syndrome
Multiple forms of dwarfism
Multiple myeloma
Multiple system atrophy
Muscular dystrophies and spinal muscular atrophies
Myasthenia gravis
Mycosis fungoides
Myeloma
Myocardial channelopathies that lead to potentially fatal arrhythmias
Myoclonus dystonia syndrome
Myopathies
Neonatal and pediatric acute respiratory distress syndrome
Neonatal cholestastic disease
Neonatal diabetes
Neonatal diagnosis of X-linked thyroid-hormone transporter disorder
Neonatal hemodialysis machine
Neonatal kidney disease
Neonatal renal failure

Rare Diseases Mentioned
Nephrotic syndrome
Neuro cancers for specific markers
Neuro ophthalmic issues
Neuroblastoma
Neurodegeneration with brain iron accumulation
Neuroendocrine tumors
Neurofibramotosis
Neurogenetics disorders
Neuroleptic malignant syndrome
Neurolipid synthesis defects
Neuronal ceroid lipofuscinosis
Niemann-Pick type C
NOMID syndrome (I have a family member with this)
Non-healing corneal epithelial defects
Non-dystrophic myotonia
Non-enterovirus, non-herpesvirus meningoencephalitis
Non-invasive devices for neurocritical care monitoring of cerebral perfusion
Non-ketotic hyperglycinemia
Non-specific interstitial pneumonitis
Nontuberculous mycobacterial infections
Normal pressure hydrocephalus
Obstructed hemivagina with ipsilateral renal agenesis
OCD
Ocular chemicalburns
Ohtahara syndrome
Organic acid disorders
Orthopedic problems associated with acromegaly
Osteogenesis imperfacta
Ovarian cancer
PAH
Panacreatic cancer
Paraneoplastic neurologic syndromes (PNS)
Parathyroid carcinoma
Pattern dystrophies of the retina
Pediatric acute kidney injury
Pediatric aplastic anemia

Rare Diseases Mentioned
Pediatric cardiomyopathy
Pediatric congenital heart disease
Pediatric epileptic encephalopathies
Pediatric Heart Disease patients
Pediatric heart failure
Pediatric immune thrombocytopenic purpura
Pediatric intractable epilepsy
Pediatric musculoskeletal and craniofacial anomalies
Pediatric OCT to measure retinal thickness in young children without the need for sedation
Pediatric solid tumors
Pediatric spinal dysraphism
Pediatric ulcerative colitis
Pediatric upper airway obstruction
Pellucid marginal degeneration
Percutaneous therapies for single ventricle heart disease
Peroxisomal disorders
Phelan-McDermid syndrome
Pierre Robin sequence
PNH
Polyarteritis nodosa
Polycystic kidney diseases
Pompes disease
Porphyria
Prader Willi
Primary Angiosarcoma of the breast
Primary biliary cirrhosis
Primary ciliary Dyskinesia
Primary hyperoxalosis
Primary immune deficiency
Primary lateral sclerosis
Primary sclerosing cholangitis
Primary spinal atrophy
Progressive familial intrahepatic cholestasis
Progressive myoclonus epilepsy
Progressive supra nuclear palsy
Prolonged persistent pulmonary hypertension

Rare Diseases Mentioned
Pseudo-obstruction
PTEN mutations
Pulmonary alveolar proteinosis
Pulmonary atresia with VSD and multiple aortopulmonary collateral arteries
Pulmonary hypertension
Pulmonary insufficiency after tetralogy repair
Pulmonary langerhans cell histiocytosis
Pulmonary valve regurgitation
Pulmonary veno occlusive disease
Pure autonomic failure
Pyoderma gangrenosum
Pyruvate dehydrogenase deficiency
Q fever
Rapid diagnostic test for microsporidia keratitis
Rapid-onset dystonia-parkinsonism
Rare bone diseases
Rare brain tumors
Rare cardiac
Rare diseases that are not diagnosed
Rare epilepsies
Rare genetic malabsorption disorders
Rare kidney stone and mineral metabolism disorders
Rare pediatric airway
Rare pediatric craniofacial syndromes
Rare tumors, such as chondrosarcoma or minor salivary gland cancers
Rasmussen's encephalitis
Reconstitution of immune deficiency disorders
Recurrent respiratory papilllomatosis
Reflex sympathetic dystrophy
Relapsing polychondritis
Respiratory chain defects
Respiratory disorders related to underlying systemic autoimmune inflammatory disorders: e.g., LIP, NSIP, COP
Respiratory failure in the newborn
Restrictive cardiomyopathy
Retinal degenerations, such as cone and/or rod dystrophies
Retinitis pigmentosa

Rare Diseases Mentioned
Retinopathy of prematurity
Rett and Rett-related disorders
Sarcoidosis
Sarcoma
Scleroderma
Sclerosis
Secondary dystonia
Serum biomarkers to indicate disease state (i.e., TSC)
Severe cerebral palsy
Severe combined immunodeficiency
Severe epilepsy of infancy
Short QT syndrome
Sickle cell
Sitosterolemia
Sjögren's syndrome
Skeletal dysplasia
Smith-Lemli-Opitz syndrome
Smoking-related ILD
Soft tissue sarcomas
Sphincter of Oddi dysfunction
Spinal AVM
Spinal muscular atrophy
Spinocerebellar ataxia
SSADHD
Stargardt disease
Stevens-Johnson syndrome
Sticklers
Sturge-Weber syndrome
Sudden sensorineural hearing loss
Surfactant protein deficiencies
Takayasu's arteritis
Tardive dyskinesia
Tetralogy with pulmonary atresia with multiple collaterals
Thallasemias
Those at risk for AML (acute myelogenous leukemia)
Thrombotic microangiopathies

Rare Diseases Mentioned
Too long to functionally list—but numerous diseases and cancers of substantial rarity
Tourette's syndrome
TP53 mutation carriers
Tracheobronchomalacia pediatric and adult
Transplantation
Transverse vaginal septum
Travel-related pathogens—rare in the U.S. but important for travelers, e.g., Japanese encephalitis virus, hepatitis E virus
TSC
TTP
Type 2 endometrial cancer
Type A carotid cavernous fistula
Tyrosinemia
Unknown diagnosis so need whole exome sequencing
Urea cycle defects
Urine creatine metabolism disorders
Urticarial vasculitis
Ushers
Uveitides
Van der Woude syndrome
Variety of pediatric oncology disorders
Vascular obstructions in children
Vasculitis
VCFS
Viral infections of the CNS, particularly in immune-suppressed patients
VLCAD deficiency for diagnosis
Von Hippel-Lindau
Wiskott Aldrich syndrome—newborn screening
X-linked retinoschisis
X-linked retinitis pigmentosa
Zellweger spectrum disorders

APPENDIX E: DIAGNOSTIC DEVICE SUGGESTIONS FOR SPECIFIED RARE DISEASES

Disease Name	Diagnostic Device Suggestion
Acute intermittent porphyria (and other acute porphyrias)	A new rapid test for urine porphobilinogen.
Acute renal failure in children	There exists a need for a minimally invasive way to diagnose acute renal failure in children. Modification of a foley catheter into a diagnostic device (instead of just a drainage tube) by placing sensors in the tubing would allow early diagnosis of acute renal failure (acute kidney injury).
aHUS	Tests are, as per excellent article by Richard Smith from Iowa, not widely available, imprecise, and not tightly correlated with clinical outcomes or response to therapy.
Alpha-1 antitrypsin deficiency	There needs to be an improvement in the testing methodology in order to assess the clinical significance or risk for disease progression in individuals.
Alpha-1 antitrypsin	Test to follow disease progression.
Alport syndrome and other genetic nephritides	Urinary test showing loss of podocytes, the best indicator of serious or progressive disease before measurable loss of kidney function.
ALS	Need biomarkers to make earlier diagnosis.
ALS	Genetic and wet biomarker diagnosis.
Alternating hemiplegia of childhood	We need to screen newborns or infants for the mutations that cause this disease. This disease is triggered by stress and has a variable phenotype.
Alternative supporting testing for immune deficiencies is dispersed across the USA and not easily available	Flow cytometry is often performed diagnostically but the rarity of the diseases means that each center often offers a small set of tests. This makes it hard to get the diagnostic testing done because it involved multiple send out labs and multiple requests for insurance approval.
Amino acid disorders	Handheld device to measure amino acid levels at home.
Amyotrophic lateral sclerosis	Tests reliably performed in blood and/or CSF that detect neurochemical biomarkers of disease activity and progression are needed to facilitate the diagnosis of ALS and for use as indicators of therapeutic response to treatment.
Amyotrophic lateral sclerosis	Biomarkers are needed.
ANCA associated vasculitis	Need an app that will incorporate lab tests, physical features, and imaging.
ARPKD	More rapid diagnosis of cases. Genetic testing often takes a long time if the insurance even allows it.
Autoimmune pulmonary alveolar proteinosis	Clinical research diagnostic tests are now available and have been validated. These tests need to be moved into clinical practice. We are attempting to do this.
Autoimmune pulmonary alveolar proteisnosis	Serum level of anti-GM-CSF autoantibody.
Biomarkers that define severity of sickle cell disease	Research funding to study the disease.
Birt-Hogg-Dubé disease	Genetic testing for FCLN gene modifications.
Bone cancers (osteosarcoma, lymphoma)	Non-invasive analysis of cells without biopsy.

Disease Name	Diagnostic Device Suggestion
Bone marrow failure syndromes	Targeted genetic diagnosis panel to identify cause of syndrome.
Bone sarcomas	Need to identify better genetic or molecular markers to tailor treatment regimens; could assess circulating tumor cells to subtype bone sarcoma histology.
BRCA1 and BRCA2	Need to identify which mutations in the BRCA1 and 2 genes which are silent, and which are clinically relevant (i.e., cause disease).
Bronchiectasis	New imaging methods that do not require radiation.
Brugada syndrome	New invasive or noninvasive measure of ventricular effective refractory period and intraventricular conduction time.
C3 Glomerulopathy	New tests to evaluate complement cascade activation.
Cadasil	More efficient genetic screening.
Cardiac sarcoid	Diagnosis often made by inference; current imaging modalities not sufficient.
Carniofacial abnormalities	A highly multiplex SNP analysis that would cover many mutations in many genes, or better yet, a dedicated DNA capture reagents and DNA sequencing of the captured genes.
Catatonia	As with the others, catatonia is difficult to diagnose and can lead to mistreatment and life-threatening situation.
CDKL5 disorder	Device for monitoring seizures.
Central apnea in newborns	Need less expensive genetic test.
Cervical dystonia	Need to establish diagnostic criteria perhaps associated with a quantitative assessment for confirmation.
Charcot-Marie-Tooth disease	Genetic testing.
Charcot-Marie-Tooth disease	Many genes need to be tested for diagnosis, which is currently very expensive and cumbersome. Lack of good genetic diagnosis limits research.
Charcot-Marie-Tooth Disease	Diagnosis is dependent on making next-generation genetic testing available and affordable to patients and the sharing of disease causing variants better available to caregivers.
Charcot-Marie-Tooth disease	Whole genome sequencing-based genetic diagnosis of CMT.
Childhood nephrotic syndrome	A test (preferably noninvasive) to provide an accurate diagnosis and prognostic information is sorely needed.
Childhood neuro disease like stroke and MS	Modifications for imaging to allow children to be more easily [imaged] without anesthesia.
Chronic exertional compartment syndrome	Noninvasive test with high sensitivity and specificity.
Chronic graft-versus-host disease	Probably will be based on biomarkers or radiology (for sclerosis).
Chronic graft-versus-host disease	At present, there are no good diagnostic tests for cGVHD. Biomarker studies are ongoing. Likewise, there are no FDA-approved therapies for relapsed/refractory GVHD. We are participating in ongoing studies of therapies for both acute and chronic GVHD.

Disease Name	Diagnostic Device Suggestion
Chronic granulomatous disease	Proteomics or metabolomics test to perform upon biopsy specimens to determine type of infection when causative organisms cannot be presumptively identified.
Chronic granulomatous disease—newborn screening	Would have to measure dihydrofolate reductase activity.
Chronic myelogenous leukemia	Need a more precise test to measure minimal residual disease (MRD). Current PCR-based tests are inadequate to definitively assess MRD.
Colon cancer	A wonderful screening test that is an alternative to colonoscopy exists, CT colonography, that is cheaper than and as accurate as optical colonoscopy. Yet the federal government refuses to pay for it, despite ample validation.
Combined immunodeficiencies	Expanding TREC testing to all states. As new immunodeficiencies continue to be described, it becomes of paramount importance to improve diagnostic techniques for these diseases. Expanding genome and targeted sequencing would be ideal.
Congenital diaphragmatic hernia	Need improved prenatal molecular imaging to understand different mechanisms that cause congenital diaphragmatic hernia; need improved prenatal genomic diagnostics to stratify severity and prognosis.
Congenital disorders of glycosylation	We need a better diagnostic test since the carbohydrate deficient transferrin may miss cases of PMM2-CDG and other subtypes.
Congenital heart diseases	Current prenatal screening with ultrasound is moderately successful in screening for congenital heart disease. For mothers that have not received prenatal care, screening with pulse oximetry prior to discharge is an improvement over no screening; however, [it] lacks sensitivity, and some infants are being discharged from the hospital with a severe underlying congenital heart disease that can jeopardize their life or result in morbidity.
Congenital hydrocephalus	Improved diagnostic imaging to determine brain injury and intracranial pressure.
Congenital limb deficiencies, tibial and fibular hemimelia	More research as to etiology of these disorders, especially environmental factors.
Congenitally inherited inborn errors of metabolism/acid oxidation defects	Need more rapid diagnostic testing.
Corneal dystrophies	Currently, diagnosis is only made on slit lamp exam. Genetic testing is typically not used because too expensive or difficulty obtaining. Consequently, we never learn what we don't know because no objective testing to see if our phenotypic diagnosis is correct. A cheap genetic test would likely demonstrate we are often misdiagnosing these conditions. Understanding what we are seeing is the first step to developing prevention and treatment short of corneal transplantation surgery.
Cornelia de Lange	Need to be able to effectively expand DNA testing to identify all clinically diagnosed cases. This is needed for a number of syndromes that cannot be confirmed with existing tests (e.g., Noonan syndrome).
Corticobasal degeneration	Neuroimaging modalities that would sensitive and specific but would require autopsy confirmation to be convincing. CSF or peripheral blood biomarkers also could be of great value.

Disease Name	Diagnostic Device Suggestion
Cowden syndrome	While we know that having a germline PTEN mutation causing Cowden syndrome confers up to 85% lifetime risk of female breast cancer, 35% for thyroid cancer, 28–32% for RCC/endometrial cancer, we still cannot predict at an individual level whether they will or will not get each of the component cancers. We need a diagnostic tool to determine organ-specific cancer risks for each Cowden syndrome person.
Crohn's arthritis	Determine assay/blood test that is diagnostic.
Crohn's disease	1. Presently, Crohn's requires diagnosis with invasive tests (endoscopy) and/or imaging studies (CT, MR, capsule). 2. Once the disease [is] diagnosed, we need to monitor disease activity, but these are expensive/invasive tests. 3. We need improved biomarkers of inflammation and/or inexpensive imaging studies.
Cystic fibrosis	I work in pregnancies complicated by CF; therefore, the primary concern is one of the diagnostic testing in the fetus, such [as] improved genetic testing in free fetal DNA maternal serum screening; improved ultrasound imaging techniques to identify markers and means of detecting fetal complications, such as bowel obstruction.
Cystic fibrosis	Sweat testing unreliable except at experienced centers. Also patients who don't have more widely recognized mutations. No specific suggestions but these are two situations which could be improved.
Cystic fibrosis	Noninvasive and reliable, inexpensive.
Cystic fibrosis (many different mutations)	Affordable genetic testing which will pick up all known and even unknown genetic mutations (since therapy is now dependent upon type of mutations).
Cystinosis	Need more rapid diagnosis in the newborn period.
Dent disease	Mutations have to be found for 20% of cases with unknown mutation to allow accurate diagnosis.
Desmoid	Would likely be a plasma-based assay. Currently, my laboratory is working on miRNA-based assays, but many other types of assays are possible, protein, other biomarkers, etc. Alternatively, improved imaging modalities would be another option, as currently available MRI/CT are inadequate.
Desmoid tumors	MR-HIFU for precise ablation of Desmoid tumor over surgical resection (high recurrence) or medications 50% response and high toxicity.
Diagnosis of myocarditis in children	Myocarditis, an acute inflammatory disease of a viral infection, for most cases remains very difficult to diagnose (and treat). Modification of MRI diagnostics may be used to dx this disease (nano-based markers to bind to inflamed myocardium). Novel biomarkers to recognize the acute myocardial inflammation associated with myocarditis.
Diagnostic techniques for sarcomas	More advanced molecular techniques for diagnostics.
Diagnostic tests for aortitis	Understand utility of MRI or PET for reliably diagnosing aortitis. Maybe new contrast agents or software for interpretation.

Disease Name	Diagnostic Device Suggestion
Diagnostic tests for various forms of vasculitis	Diagnostic tests to determine disease activity in vasculitis. For example, a blood or urine test to determine if a patient has active glomerulonephritis. Diagnostic test for eosinophilic granulomatosis with polyangiitis or other rare forms of vasculitis.
Dyskeratosis congenita	Telomere length assay, in combination with functional assay, such as measurement of oxidative stress or DNA damage responses.
Dystonia	There are too many individual genetic tests for multiple subtypes of dystonia. Whole exam sequencing can solve this problem, at a lower cost than testing each gene. Again, insurers rarely cover the costs, so they are not conducted.
Dystonia	Need more genetic tests to diagnose forms of dystonia. I expect with refinement of DaTscan (used in Parkinson syndromes), might be useful in diagnosis of dystonia.
Dystonia	For dystonia, there is currently no diagnostic test for this disorder and therefore only a subjective evaluation making the diagnosis somewhat soft.
Early accurate intrauterine diagnosis of congenital heart disease and treatment	High-resolution echocardiography.
Early onset scoliosis	Genetic testing to determine what type of scoliosis will progress or resolve.
Easily obtainable test for speciating acanthamoeba	Acanthamoeba have been speciated based on morphology of trophozoites and size of the cysts. A DNA-based test could potentially speciate acanthamoeba, I believe.
Ebola and other viral hemorrhagic diseases	We need a highly sensitive (99%) and specific (99%), very rapid (1 hour), molecular-based assay for Ebola and similar viruses.
Ebstein's anomaly	Improved cardiac MRI.
Ebstein's anomaly	Would like diagnostic testing to provide more information about the likelihood of success with single- versus two-ventricle surgical approach.
Ehlers-Danlos disease	Expansion of genetic testing to diagnose the disorder and consideration of utilizing a CT protocol to look at vascular lesions that might help secure the diagnosis.
Emerging or re-emerging pathogens (e.g., adenovirus type 14)	Any of the common real-time PCR platforms.
Eosinophilic colitis	Need an alternative to endoscopy as described previously.
Eosinophilic colitis	Diagnostic criteria are lacking. The ability to distinguish EC from IBD, etc., must be created.
Eosinophilic esophagitis	EoE needs a noninvasive method for disease surveillance. Though the string test may soon be emerging (to count eosinophils), the most important need in EoE is to noninvasively monitor esophageal fibrosis.
Eosinophilic esophagitis	We need a non-invasive device to monitor esophagitis.
Eosinophilic esophagitis	Something that can be done in the office without the need for anesthesia or sedation that could be well tolerated by children and adults alike.

Disease Name	Diagnostic Device Suggestion
Eosinophilic esophagitis	Need for a test that is noninvasive to diagnose and monitor eosinophilic esophagitis.
Eosinophilic esophagitis	Modify current endoscopes to obtain deeper mucosal biopsies safely. Such endoscopes are in use in Europe.
Eosinophilic esophagitis	Minimally invasive method to obtain intestinal tissue.
Eosinophilic esophagitis	Eosinophilic esophagitis is a chronic inflammatory disease of the esophagus caused by repeated exposure to specific foods. No testing currently exists to delineate which foods patients need to eliminate without eliminating foods unnecessarily, which is the current state of care.
Eosinophilic esophagitis	Enterotest.
Eosinophilic esophagitis	EndoFlip for EoE.
Eosinophilic esophagitis	Creating a non-invasive approach to diagnose/monitor EoE.
Eosinophilic esophagitis	Assessment of functional impairment of the esophagus.
Eosinophilic esophagitis and eosinophilic gastrointestinal disorders (in general)	1. Transthoracic scan (e.g., ultrasound, PET, MRI) capable of identifying evidence of eosinophilic disorders in EoE, as the other EGID are quite low frequency, and would be difficult to identify features consistent with disease. 2. Biomarker.
Eosinophilic gastritis	Diagnostic criteria are lacking.
Eosinophilic gastroenteritis	Non-invasive disease monitoring. Food allergy testing.
Eosinophilic gastroenteritis	Minimally invasive tool to capture intestinal tissue and contents.
Eosinophilic gastrointerestial disease	A non-invasive marker and test for diagnosing and follow up of patients is needed. The use of repeated endoscopy is expensive and has risk.
Eosinophilic gastrointestinal disorders (EGID)	Currently, diagnosis can only be made through use of endoscopy. A serum test that can measure eosinophil tissue activity in tissues, such as the esophagus, would improve the time to diagnosis as well as response to management.
Eosinophilic GI disease	There is an overwhelming need for a novel noninvasive biomarker to both diagnose and monitor response to treatment in EGID.
Eosinophilic granulomatosis with polyangiitis (Churg Strauss)	Better serum tests for diagnosis would be helpful. Potentially, markers related to eosinophil function may be helpful.
Esophageal adenocarcinoma	We need non-endoscopic modalities for screening for esophageal adenocarcinoma.
Ewing sarcoma	DNA or molecular testing. Currently, electron microscopy is used in difficult cases.
Extreme microcephaly	Prenatal imaging to identify affected fetuses and aid in prognosis and understanding of mechanism of microcephaly.
Fabry's disease	A better and more rapid screening test to discern carrier versus homozygous patients.

Disease Name	Diagnostic Device Suggestion
Familial exudative vitreoretinopathy (FEVR)	Early and frequent examinations are needed to evaluate the retinal status. Genetic testing is not definitive. Need more definitive genetic tests for FEVR and need better method for peripheral retinal examination without general anesthesia. This might be via modified indirect ophthalmoscopy not using visible light. This might also be through wide-field optical coherence tomography, potentially with OCT angiography, which could identify vascular flow without dye injection in young children.
Familial LCAT deficiency	Assay for LpX.
Familial Mediterranean FEVR	Practical, readily available and simple blood test.
Far more accurate clinical staging of esophageal cancer—a rare disease—that affects treatment decisions	Early-stage cancers are under staged, leading to inadequate cancer resection, and advanced cancers are over staged, which is not yet bad. We need more accurate imaging but also either new biomarkers, molecular or genetic profiling that will aid in adequate and more targeted and specific (and less toxic) treatment.
Fatty acid oxidation disorders	There are two needs. Rapid molecular testing to confirm diagnosis in the newborn setting. The second is a point of care enzymatic test for use in settings where rapid access to tertiary care centers is not available.
Focal dystonia	Better diagnostic instruments and better severity measures.
Focal dystonia	Better genetic tests.
Focal segmental glomerulonephritis	Blood test? Kidney biopsy needed at present.
Focal segmental glomerulosclerosis	We need a test that differentiates primary from secondary FSGS.
Focal segmental glomerulosclerosis	The kidney biopsy shows FSGS, but it is impossible to determine whether it is primary (or having an immunological basis for the disease) or secondary (or non-immunological). The current test of albumin permeability cannot be scaled up for routine use. There is implication of these tests for recurrence of the disease following transplantation.
Focal segmental glomerulosclerosis	Better approaches to kidney biopsy.
FOXG1 disorder	Device for identifying seizures.
FSGS	Identification of non-invasive predictors of disease progression as surrogate markers for clinical trial. Validation of proteinuria as clinical outcome.
FSGS	Combination of histological diagnosis, ApoL1 risk allele stratification, transcriptome analysis of kidney biopsies, digital pathology, and cell-based assay.
Gaucher's disease	One that enables earlier and definitive diagnosis as part of a “routine” anemia broad screening tool.
Generalized dystonia	The development of diagnostic criteria and perhaps a clinically practical device that assesses motor function, loss of central inhibition, etc.

Disease Name	Diagnostic Device Suggestion
Genetic causes of aortic dissection and aneurysm	Genetic testing to identify currently undiagnosed genetic causes.
Genetic diagnoses of primary immunodeficiency disorders	Expand next generation gene panels. Currently WES is available, would upgrade to WGS.
Genetic disorders of surfactant metabolism in newborn infants	Need a paracorporeal lung device for maintenance of lung function; need device to permit genome editing targeted to pulmonary epithelial stem cells for correction of mutations in surfactant associated diseases; need prenatal testing to identify affected fetuses.
Genetic epilepsy syndromes	Adults lack insurance coverage for genetic testing and can't afford to pay for testing.
Genetic glomerulopathies	Glomerulopathies are still currently diagnose by renal biopsy assessment, which is insufficient to provide information other than a morphologic description.
Genetic neurological disorders	There are a large number of undiagnosed neurological disorders with likely a genetic basis or inflammatory basis. Improving genetic analysis will aid in more precise diagnosis.
Genetic test gin for many immune deficiencies is not available except through WES, which many insurance companies will not pay for	Can do targeted sequencing (capture primers specific for immune deficiencies).
Genetic testing for rare abnormalities like polycystic kidney disease	Need less expensive genetic testing for newborn and parents.
Giant cell arteritis	There is an urgent need for better diagnostic tests than a temporal artery biopsy, which is relatively invasive and not as sensitive as it needs to be.
Glutaric aciduria	Modification of tandem mass spec.
Graft-versus-host disease	We need more reliable biomarkers for GVHD, acute and chronic, as well as predictive biomarkers to gauge the chance of successful treatment.
Graft-versus-host disease after allogeneic hematopoietic cell transplantation	Panels testing biomarkers, though biomarkers have not been established completely.
Granular corneal dystrophy	We need much more easily and rapidly performed and cheaper genetic testing.
HD	Multiple markers of active disease yet the diagnosis remains on clinical ratings of a movement disorder, when other signs and symptoms and brain scans show disease 15–20 years earlier.
Heart failure in small children	More data regarding usefulness of current diagnostic (BNP, etc.) for predicting outcomes in small children.
Heart failure with preserved ejection fraction	Identify genetic marker that differentiates HFpEF with limited long-term survival that would allow increased priority on transplant waiting list.
Hemophilia	A more simple testing method for factor levels.
Heparin-induced thrombocytopenia	Current diagnostic tools are not adequate, as you have to combine several different tests to optimize the diagnosis, yet it is not very accurate.

Disease Name	Diagnostic Device Suggestion
Hereditary angioedema	Type 3 HAE has normal C1INH levels. Something that more clearly shows that it is bradykinin-based angioedema is needed.
Hereditary angioneurotic edema (C1 esterase inhibitor deficiency)	The severity and clinical manifestations of the swelling episodes are not predictable simply by the measurement of quantity or activity of the C1 esterase inhibitor. A more specific methodology to assess the clinical significance would be helpful.
Hereditary pancreatitis	Again, I would create a DNA capture reagent to pull down all of the genes that have been associated with HP, and then perform DNA sequencing on the captured DNA.
Hereditary retinopathy	Rapid genetic tests.
Heritable pulmonary arterial hypertension	A more complete genetic screen.
Hermansky-Pudlak syndrome	Platelet electron microscopy is considered the gold standard but is not readily available to clinicians and requires send-out for specialized expertise. Genetic testing is expensive and not available to all patients.
Hermansky-Pudlak-diagnostic platelet assay	Currently, the diagnosis of HPS is made by electron microscopy of platelets, looking for absence of dense granules. That is a clunky and expensive approach. It could easily be replaced by an assay looking for absence of dense granule products in isolated platelets.
HHT	HHT is angiogenic condition caused by telangiectasia formation. Anti-angiogenic therapies, which are used for cancer, may be useful, including bevacuzimab, sirolimus, sutent, paclitaxel, and others. These could also be coated onto devices to improve endovascular treatment options, which are used to treat brain and lung AVMs.
Huntington's chorea	Reliable, inexpensive, noninvasive.
Huntington's disease	Improve diagnostic sensitivity and specificity in premorbid or early phase of disease.
Huntington's disease	Cognitive/neuropsychological tests have been shown, in research, to identify the development of HD decades before the motor signs present. These tests need to be examined more closely and refined to improve their accuracy.
Huntington's disease	Not certain of specifics, but dilemma in HD is when to classify patient with clinically manifest disease (given variable phenotype). An imaging or biomarker that reliably identifies clinically manifest disease would be helpful (a progression biomarker would also be helpful).
Hyperammonemia	A device to reliably measure ammonia at the bedside and at home, as this level is critically important in determining immediate therapeutic measures.
Hypersensitivity pneumonitis	Improve bronchoscopic biopsy or obtain serologic testing for disease.
Hypersensitivity pneumonitis	Blood test to diagnose hypersensitivity pneumonitis.
Hypertrophic obstructive cardiomyopathy	We need better genetic tests and diagnostic tools for this disease.
Hypobetalipoproteinemia	Need a genetic test to rule in or rule out an apoB mutation.
IBM	Blood test to identify specific IBM biomarker.

Disease Name	Diagnostic Device Suggestion
Identification of anomalous origin of a coronary artery, and its impact on sudden death	A simple, but highly accurate, non-invasive test that can be applied essentially to all children, and, in particular, any child involved in athletics.
Idiopathic intracranial hypertension	Non-invasive intracranial pressure monitor.
Idiopathic nephrotic syndrome	Non-invasive test for podocyte dysfunction and urinary podocyte loss. Test based on urine specimen and reproducible.
Idiopathic pulmonary fibrosis	Biopsy may be improved and especially for those that were never biopsy tested and may need a less invasive test, that are elderly and degraded by the disease, to help determine the type of fibrosis from the zoo of fibrosis types and the possible cause to help provide a greater solution for possible treatment or, ideally, cure.
Idiopathic pulmonary fibrosis	Blood test to diagnose disease. (Currently requires invasive lung biopsy that some patients cannot undergo.)
Idiopathic pulmonary fibrosis	Biologic fluid-based test.
Idiopathic pulmonary fibrosis (IPF)	We need a blood test to diagnose IPF.
Idiopathic retroperitoneal fibrosis	Biopsy of retroperitoneal tissue with staining for IgG 4 antibodies if such staining is available.
IgA nephritis	Identification of non-invasive predictors of disease progression as surrogate markers for clinical trial. Validation of proteinuria as clinical outcome.
IgA nephropathy	Kidney biopsy needed to diagnose IgA nephropathy.
Implant-related hypersensitivity	Synovial fluid test.
Inborn errors of metabolism	Hand-held device for measuring blood ammonia, preferably without the need of blood sampling.
Inflammatory breast cancer	Inflammatory breast cancer (IBC) is a clinical diagnosis. Many patients are misdiagnosed as having infection of the breast.
Inflammatory conditions of the lower urinary tract	Assess urinary and bladder wall elements for markers for condition and responsiveness of same to interventions.
Inherited ataxias	Improve accessibility and quality of genetic testing (such as a specified WES protocol).
Inherited retinal dystrophies	There should be a screening panel of molecular genetic testing to allow broad testing in a cost effective manner. At the present time, testing is piecemeal and very expensive and not typically covered by insurance.
Interstitial lung disease	Currently lung biopsy required for diagnosis; need a less-invasive approach.
Interstitial lung diseases	We are in need of biomarkers to complement the current HRCT/histopathology diagnosis.
Interstitial lung diseases	Noninvasive means of defining underlying cause, determining treatment, and prognosis.
Intraocular lymphoma	Need to improve the diagnostic yield from vitrectomy samples of small volumes of fluid.

Disease Name	Diagnostic Device Suggestion
Isolated, idiopathic dystonia	Better clinical diagnostic criteria that would be generalizable to the relevant clinicians. This could be clinical criteria, examination findings, neuroimaging, or potentially biomarkers in blood or CSF.
Jarcho-Levin syndrome	Refining the genetic test for Jarcho-Levin to determine which variants go on to moderate restrictive lung disease (so do not need treatment) versus those with severe restrictive lung disease that need surgery early in life.
Jeune	Specific genetic testing that distinguishes Jeune [patient] that will go on to improved chest growth with survivable restrictive lung disease versus those with lethal RLD that requires surgery.
Kernicterus	We desperately need a new diagnostic tool—even a [thorough] questionnaire—for diagnosing new cases of Kernicterus so patients can get early care.
Krabbe disease	Multivariate or mutiparametric analyses.
LAM	Sensitive serum biomakers.
LAM	Need VEGFD more widely available. Also even better diagnostics would be nice.
Laminin deficiency	Currently, genetic testing is available, but unclear who needs it. Need screening test for increased risk of SCD.
Larsen's syndrome	Easy genetic testing.
Laryngeal dystonia	Diagnosis is based on perception of voice. More objective testing would be helpful.
LCAT deficiency	Need a way to measure lipoprotein X.
Leber's congenital amaurosis and other rare optic neuropathies	Investigation is needed into functional tests (e.g., tests of color vision, dark adaptation) that can supplement objective tests (e.g., ophthalmoscopy) in diagnosis.
Lesch-Nyhan disease	There are good diagnostic genetic tests. The major problem is getting insurers to cover them. As a result, many clinicians use cheaper but less useful tests.
Leucoencephalopathies	Develop or adapt MR imaging to better determine structure/function relationships in patients.
Leukodystrophies with the exception of adrenoleukodystrophies	Efficient genetic testing have to be more available.
Lipodystrophy	Need genetic screening and better awareness of who to test.
Long QT syndrome	We describe only a fraction of the genotypes for LQTS, and in the case of this disease, unlike many others, genotype does inform treatment. We need additional testing for unexplained phenotypes.
Low-grade chondrosarcoma	To create a test to analyze the DNA sequencing of the nucleus of the biopsied tissue, so we can easily differentiate it from benign enchondroma.
Lupus	Blood work.
Lymphagioleiomyomatosis	Need better non-invasive test for diagnosis short of lung biopsy. Also don't have great measure of disease progression. Serum vegf-D is a good start but isn't elevated in all cases.
Lymphangioleiomyomatosis	We need a genetic test for LAM or an improved blood test to diagnose LAM

Disease Name	Diagnostic Device Suggestion
Lymphangioleiomyomatosis	VEGF-D blood test.
Lymphangioleiomyomatosis	The current utility of VEGF-D serum assay is limited because about 50% of current LAM patients have normal numbers and the test is administered in a single laboratory in the US. New diagnostics are needed for bronchoscopy tissue samples or other blood tests that would require an RFA. Note that in general, venture capital is not very keen on diagnostic tests.
Lymphangioleiomyomatosis	Serum VEGF-D is available in one CLIA lab but as an ELISA. A goal would be for it to be modified to a format that could be more widely available.
Lymphangioleiomyomatosis	Serum level of VEGF-D, no GLP kit, no insurance covered.
Lymphangioleiomyomatosis	Right now we use a combination of imaging, blood (VEGF-D), and biopsy. One test that is non-invasive would be ideal.
Lymphangioleiomyomatosis	Need better diagnostic tests, better biomarkers for disease progression, better therapies.
Lymphangioleiomyomatosis	Need a more sensitive diagnostic biomarker.
Lymphangioleiomyomatosis	Blood tests to diagnose the disease are most desirable, although improved ability to detect with BAL or transbronchial biopsy of the lung would also be an improvement.
Lymphangioleiomyomatosis	Blood screen that would be additive to VEGF-D.
Lymphangioleiomyomatosis	Better genetic testing is needed for disease diagnosis. Disease-specific biological markers are also needed to assist in disease diagnosis, as well as for disease activity monitoring and assessment of response to therapy.
Lymphangioleiomyomatosis	A breath test would be ideal if sufficiently specific and sensitive.
Lymphangioleiomyomatosis	A blood test is available but not sensitive for this disease. A peripheral blood test (or genetic test) is needed for diagnosis.
Lymphangioleiomyomatosis—FDA-approved diagnostic VEGF-D assay	Validate the existing R&D kit and obtain FDA approval so the kit can be sold and made commercially available. Currently it is performed in boutique CAP/CLIA lab and is difficult to order.
Lymphangiomatosis	There only current test to diagnose lymphangiomatosis requires tissue biopsy and pathological analysis. A useful biological test is needed to be used for either primary diagnosis or for monitoring and management of disease status.
Lymphangiomatosis	The test which check serum VEGF-D of patients may be a diagnostic test for lymphangiomatosis. If the CT scan of one patient suggests probable LAM, and the concentration of his serum VEGF-D 800 pg/ml. I consider the diagnosis of the patient is definite LAM.
Lymphangiomyomatosis	Blood biomarker. Improved imaging.
Lynch syndrome	Better detect DNA mismatch repair deficiency, regardless of whether it is mutation, DNA methylation (more common than mutation) and not confounded by difficulties interpreting genetic variants.
Lysosomal storage diseases	Panel testing that is cheap and fast for diagnosis (newborn screening multiplex panel).

Disease Name	Diagnostic Device Suggestion
Mal de débarquement syndrome	I don't have any suggestions other than to say that we need improved tools to assess dysfunction in central processing of vestibular information.
Malignant hyperthermia	Don't have a good idea for a device, but muscle testing is too difficult and costly. Genetic testing is probably the future, but currently, it is very specialized and not easily available. Broadly available, broad panel, genetic screening, for rare disorders that affect anesthesia and surgery would be optimal (e.g., MH, muscular dystrophies, abnormal pseudocholinesterase).
Many tropical infections (e.g., loa loa)	There currently is no FDA-cleared test that can distinguish between the many filarial diseases. Disease-specific testing is needed.
Marfan syndrome aneurysms	Determine the optimal stent graft to treat these patients.
Mastocytosis/mast cell activation syndrome	A tryptase seems to miss most MCAS and bone marrow is very invasive and not always easy to obtain.
Melanoma	A test that would better predict prognosis and response to therapy test to identify nodal involvement without surgery.
Meniere's disease	Potentially imaging MRI variations.
Mesenteric venous thrombosis	Noninvasive intraoperative monitoring device or technique that can be used during laparoscopy.
Metabolic disorders	We need a newborn screening test to identify MPS diseases amenable to curative allogeneic bone marrow transplantation, prior to onset of symptoms.
Minimal change disease	Identification of non-invasive predictors of disease progression as surrogate markers for clinical trial. Validation of proteinuria as clinical outcome.
Minimal change disease	1) Blood or urine test, possibly directed against putative cytokine or other factor 2) Some characteristic of selective proteinuria typical of MCD
Minimal residue disease (MRD)	Flow cytometry method has been developed for diagnosis of MRD; however, standardization of the flow cytometry assay procedure needs to be worked out to achieve reproducible and comparable results in hospital and clinical setting.
Mitochondrial disease	Current testing is limited to genomic analyses and biochemical analyses in tissues/cells. Need in vivo functional testing to evaluate for mitochondrial disease.
Mitochondrial diseases	Need [an] integrated test using NEXT-gen DNA testing, together with new biomarkers.
Mitochondrial diseases	I am working on a grant application for this—cannot discuss.
Mitochondrial disorders	The identification of patients with mitochondrial diseases is problematic. No really effective screening tests exist and many patients are subject to expensive and time-consuming DNA testing.
Mitochondrial disorders	Functional testing is required to determine the significance of detected variants of unknown pathogenicity. In addition, further biomarkers or imaging techniques are needed in order to evaluate the degree of mitochondrial impairment in patients, and response to therapies.
Mitochondrial disorders	Better biomarkers to be used in the diagnosis of patients with mitochondrial disorders

Disease Name	Diagnostic Device Suggestion
Mitochondrial respiratory chain deficiency	There is no reproducible wait to measure respiratory chain activity in tissue samples, ideally easily obtained ones like WBCs. Also molecular diagnostic testing is cumbersome. Targeted panels are incomplete and exome is slow.
Moderate and severe pediatric traumatic brain injury	MRI needs to be faster, easier to hold children still/comfortable, and/or with cost-effective MRI-compatible distraction (e.g., video).
MODY	The existing test needs to be more widely available so that we can screen more individuals. Currently, it is not covered by insurance and is expensive.
MODY as a form of T2DM	MODY requires genetic suspicion in young patient with T2DM, with a strong family history of diabetes. Aberrant genetic state is present. Commonly known, but not frequent enough to trigger suspicion by physician. Easy means of identifying MODY. See University of Chicago experience.
Motility disorders of the intestinal tract	Something needs to be developed that does not involve intubation of the small bowel or colon.
Mucopolysaccharidoses (newborn screen)	Adaptation of newborn screening cards to detect these conditions.
Mucopolysaccharidoses in adults	As with channelopathies, the ready availability of a rapid test would be useful. I do not know how current testing would need to be modified.
Mucopolysaccharidoses, e.g., Hurler's needs newborn screening	Use of blood spot to detect either alpha iduronidase or elevated glycosaminoglycans.
Mucopolysaccharidosis	Testing gait with the use of wireless sensors.
Mucus membrane pemphigoid	Biopsies with immunofluorescence not reliable, need better test of tissue sampling.
Muir Torre	Need a quick test to help identify.
Multiple congenital anomaly syndrome	Takes 2–4 months to get a genome wide array result leading to delay in diagnosis and potential treatment.
Multiple myeloma	Rapid diagnosis with minimum invasiveness.
Multiple myeloma	Flow cytometri panels for diagnosis and minimal residual disease monitoring have been developed and validated but do not have FDA approval and therefore cannot be produced by manufacturers and sold. This leaves labs concocting their own cocktails, with occasional mistakes [potentially] having disastrous impact on patient care. Specialized software is available to assist in analysis but is not FDA-approved and can't be marketed as such.
Multiple myeloma	Need better testing to replace the current evaluation of radiography, bone marrow biopsy, SPEP, UPEP, etc. It's too complicated in the current state.
Multiple myeloma	Less painful bone marrow sampling.
Multiple system atrophy	The combination of 7-T structural MRI and Florbetaben (18F) PET imaging could provide a diagnostic test/protocol that would differentiate MSA from clinically similar diseases.
Muscular dystrophy	Ease of doing genetic testing without cost limitations.

Disease Name	Diagnostic Device Suggestion
Myocardial channelopathies that lead to potentially fatal arrhythmias	Identification of these abnormalities requires genetic testing. Such tests are very time consuming, usually must be sent to distant laboratories (and are expensive). A test that is readily available and rapidly performed would be an advance.
Myopathies	A blood test or immune-staining muscle biopsy technique which differentiates different myopathies from each other.
Narcolepsy	Presently, narcolepsy is treated solely using medications, which can have considerable side effects. Deep brain stimulation (DBS), when strategically placed and with appropriate stimulus parameter adjustments, might enhance alertness. Systematic surveys of sleepiness levels (before and after DBS placement) should be mandated in order to determine if alertness can be enhanced with this device.
Neonatal and pediatric acute respiratory distress syndrome	Continuous automated assessment of lung function and possible deterioration using a computerized system. The system would detect changes in lung function that would precede the obvious clinical hall marks of PARDS.
Neonatal kidney disease	If a biopsy is needed, a smaller needle would be helpful, rather than having to do an open procedure.
Neonatal renal failure	Need better more specific measures of renal function. Increase serum creatinine is late finding.
Nephrotic syndrome	We need greater specificity in our testing of nephrotic syndromes so that we may better tailor treatment according to the phase of disease.
Nephrotic syndrome and glomerulonephritis	Unified approach to genetic screening, as well as biomarkers to predict underlying mechanism.
Neuroblastoma	F-DOPA PET or other PET radiopharmaceuticals needing FDA approval for this indication.
Neuroendocrine tumors	Use of Ga-DOTA-TOC or DOTA TATE PET imaging; these require FDA approval of Ga-DOTA-TOC or DOTA TATE.
Neurofibromatoses	Testing currently depends upon imaging studies and genetic studies for NF gene. Both of which are expensive and not always available.
Neuroleptic malignant syndrome (NMS)	NMS is difficult to distinguish from other conditions and can be life threatening, so it would be useful if there was a device that could centrally determine the cause of the symptoms and target treatment on NMS quickly.
Neurolipid synthesis defects	New group of disorders most of which are now diagnosed via exome sequencing. Need a rapid, reliable biochemical approach (lipidomics).
Neuronal ceroid lipofuscinosis	Rapid identification of lysosomal storage material.
NOMID syndrome	Something simpler than chromosome analysis.
Non-invasive test for EoE	Salivary test.
Non-dystrophic myotonia	Easy to access genetic testing of all mutations known to cause NDM.
Non-invasive devices for neurocritical care monitoring of cerebral perfusion	Optical device for measuring cerebral perfusion (diffuse correlations spectroscopy) and cerebral oxygen metabolism (frequency or time domain NIRS).

Disease Name	Diagnostic Device Suggestion
Non-ketotic hyperglycinemia	Faster and more comprehensive gene testing that does not require months to perform sequential steps in trying to finalize the diagnosis and aid families in genetic counseling who may require this soon after the identification of a child with NKH.
Nontuberculous mycobacterial infections	More rapid and specific molecular assays for diagnosis, speciation, and drug susceptibility tests
Normal pressure hydrocephalus	Because the underlying pathophysiology is poorly understood, this is difficult. A non-invasive measure of brain compliance has been suggested. Current tests are insufficiently sensitive.
Obstructed hemivagina with ipsilateral renal agenesis	Similar comments to my comments on transverse vaginal septum. OHVIRA requires earlier diagnosis with sensitive imaging to prevent retrograde menstruation and tubal damage.
Orthopedic problems associated with acromegaly	Decrease bending modulus of hip implants; create new attachment interfaces.
Osteogenesis imperfacta	Assay or test that will make an exact diagnosis and indicated the severity of the disease.
Osteosarcoma	Blood test or screening test.
Ovarian cancer	Screening test for women at risk using serum or other body fluid.
Ovarian cancer	Need noninvasive biomarker or genetic assessment.
Pancreas cancer	Once pancreas cancer is detectable by either CT or EUS, it is generally incurable. If there was a diagnostic test (blood test) that could help with earlier detection, that may help to manage it prior to development of metastatic disease.
Pancreas cancer	I don't know but need an accurate method for early detection, with high sensitivity and noninvasive. Blood test/tumor markers/genetic screening would hone helpful.
Pancreas cancer	Improve diagnostic biopsies.
Pancreatic cancer	Something is needed to give a positive screening.
Pancreatic cancer	Need an inexpensive, noninvasive, reliable test.
Pancreatic cancer	We need something that identifies the presence of pancreatic cancer when the primary tumor burden is microscopic. Will likely require a molecular diagnostic capable of detecting circulating tumor cells or proteins/biomarker in plasma.
Pancreatic cancer	Increasing sensitivity and specificity of blood tests and those of other body fluids. Explore breath analysis.
Pancreatic cancer	Early diagnosis depends upon development of either a sensitive/specific blood or stool marker or the ability to screen at regular intervals.
Pancreatic cancer	A blood test that could screen for some blood-borne marker would be ideal.
Pancreatic cancer	Need some device that would pick up cancer before morphologic changes.
Pancreatic cancer	Two approaches are possible: one is a hematologic test, and the other is improved anatomic visualization or conspicuity on the existing imaging platforms.

Disease Name	Diagnostic Device Suggestion
Pancreatic cancer	Very difficult to diagnose early. Need either a blood test (ideal) or an imaging approach that is noninvasive and diagnostic.
Pancreatic cancer	It would be best to have a non-invasive, such as blood test, that can diagnose pancreatic cancer in an early, resettable stage.
Pancreatic cancer	Early diagnosis is essential for pancreatic cancer. Most disease is diagnosed too late for effective intervention. Early diagnosis will need to be able to detect the disease before it becomes symptomatic.
Pancreatic cancer	At the time of diagnosis, the great majority of pancreatic cancers have already spread. Current imaging modalities can detect a lesion only when large enough or with sufficient difference in vascularity or cell density to allow identification. A targeted contrast or radiopharmaceutical agent that will enhance detection or perhaps a blood test that might detect some altered blood product or cell marker could be considered.
Pancreatic cancer	Biomarkers or noninvasive imaging screening program.
Pancreatic cancer	A chemical test to get early diagnosis of pancreatic cancer.
Pancreatic cancer	Genetic profile or gene expression, something you can test in blood or spit or stools or urine.
Pancreatic cancer	A sensitive and specific blood or urine test for early diagnosis of pancreatic cancer [PCa].
Parathyroid carcinoma	Be able to diagnose the carcinoma prior to intervention.
Parkinson's disease	Parkinson's disease is a condition diagnosed largely on clinical grounds. A functional imaging scan is said to have a high level of sensitivity to diagnosis, though I don't feel superior to clinical diagnosis. A more sensitive and specific scan would be very helpful in diagnosis.
Pathologic myopia	Current imaging devices do not work reliably or reproducibly on elongated eyes in pathologic myopia.
Pattern dystrophies of the retina	Need reliable and reproducible automated imaging to identify and differentiate from age-related macular degeneration, including rapid genetic testing.
Pediatric acute kidney injury	Current diagnosis is very delayed, and that hampers our ability to provide effective therapy in a timely manner. We need diagnostic devices (biomarkers) that allow us to make the diagnosis early.
Pediatric congenital hydrocephalus	Better endoscopic technology for performing endoscopic third ventriculostomy and choroid plexus cauterization. Improved shunt technology that resists failure. Improved diagnostic test to determine whether hydrocephalus is optimally treated and/or for early detection of treatment failure. Non-invasive technique to measure ICP.

Disease Name	Diagnostic Device Suggestion
Pediatric congenital heart disease	Need new blood or urine based biomarkers that can be performed in the pregnant mother to identify congenital heart disease prior to delivery. The existing method of fetal echocardiography is not sufficient and many children are still born with life-threatening congenital cardiac disease without prenatal diagnosis.
Pediatric OCT to measure retinal thickness in young children without the need for sedation	This device gives a more accurate measurement of the retinal thickness in both adults and pediatrics. It would be ideal to monitor for adverse effects of medications. It does require sedation in infants/toddlers.
Pediatric solid tumors	Improve tools for needle core biopsy.
Pediatric spinal dysraphism	Similar to prior questions on traumatic brain injury—MRI is the test of choice, but for this indication is a long study requiring sedation in many children. Something shorter and/or administered with appropriate distraction techniques would make this test easier and less risky to get and with higher yield.
Pediatric upper airway obstruction	Modification of existing technologies which use non-invasive sensors to detect and quantify the severity of upper airway obstruction and monitor improvement with therapies. This can apply to acute upper airway obstruction in intensive care units, or more chronic diseases related to anatomic or functional status of the patient (i.e., airway anomalies).
Percutaneous therapies for single ventricle heart disease	Implantable pump in the Fontan pathway. Fontan pressure monitoring. Percutaneous Fontan completion. Diagnostic tests for progressive liver dysfunction in Fontan patients.
Pierre Robin sequence	Faster screen for mutations in Stickler/Col2a.
Pompes disease	New testing is needed to allow for immediate and long-term therapy for newborn/pediatric patients. Testing with more rapid turnaround will allow plans for transplant/medical therapy/palliation.
Porphyria	Biochemical testing has to be done when the patient has symptoms, and then the patient is asked to mail a urine sample back to the lab for testing. Porphyrins are light sensitive, so if the patient exposes the sample to light, then the testing might become negative before testing could be performed. A non-light-sensitive test, or a test that could give immediate results, would yield better diagnostic accuracy and perhaps capture patients that would otherwise be missed.
Porphyrias	The currently available tests require that patients be in a crisis in order to be diagnosed. We need a more sensitive/specific test that can be used in between attacks.
Porphyrias (all types)	Obtaining the biochemical test results (specifically porphobilinogen, aminolevulinic acid, total porphyrins) in a shorter time period will help significantly with making a diagnosis. Despite having a PBG rapid test, this examination is too cumbersome to use—particularly if the disease condition is rarely encountered.
Prader Willi	Need a rapid diagnostic assessment, as this is most common congenital hypotonia with different outcomes to other.

Disease Name	Diagnostic Device Suggestion
Predicting and preventing SAH-associated cerebral vasospasm and stroke	Biomarkers.
Predicting risk of rupture in intracranial aneurysms and AVM	I think this will be a combination of conventional imaging and biomarkers.
Pre-symptomatic muscular dystrophies	Don't have a good idea for a device, but muscle testing is too difficult and costly. Genetic testing is probably the future, but currently, it is very specialized and not easily available. Broadly available, broad panel, genetic screening, for rare disorders that affect anesthesia and surgery would be optimal (e.g., MH, muscular dystrophies, abnormal pseudocholinesterase).
Primary (inherited) immunodeficiencies	Targeted genomic panel to identify genetic cause.
Primary biliary cirrhosis	10%of patients with PBC are AMA negative. More than half of these patients are ANA positive. There is a type of ANA that is PBC-specific—that includes anti-gp210 and anti-sp100. Others are being developed. We need to have those tests commercially available. In the absence of these tests, we have to perform a liver biopsy. And even that may not be diagnostic.
Primary ciliary dyskinesia	Modification (primarily software, not so much hardware) of FDA-approved exhaled NO devices
Primary ciliary dyskinesia	The current nasal NO device used for help screen for PCD desperately needs FDA approval.
Primary ciliary dyskinesia	Studies have consistently demonstrated that individuals with PCD have low nasal nitric oxide (NO) levels. The current NO analyzers available commercially are not approved by the FDA for PCD diagnostic testing. Nasal NO measurements are still primarily performed as part of research studies. We desperately need the FDA to review and approve current NO analyzers, particularly one from EcoMedics, for use to measure NO in individuals suspected of having PCD.
Primary ciliary dyskinesia	Nasal nitric oxide is a critical screening/diagnostic test. Currently, it requires a chemiluminescent device that costs ~$70,000 and is available only at a few centers. It also is not yet FDA approved and needs to be. The hand-held inexpensive devices widely available to measure exhaled nitric oxide could likely be adapted to measure nasal nitric oxide.
Primary ciliary dyskinesia	Modify devices used to measure exhale nitric oxide to measure nasal nitric oxide—adaptation has been done but not FDA approved and no CLIA-approved testing
Primary ciliary dyskinesia	Currently available device to measure nasal nitric oxide is NOT FDA approved and therefore there are significant limitations to availability of this technology for screening diagnostic purposes. Further, the nasal probes may not be suitable for use in very young infants and children.

Disease Name	Diagnostic Device Suggestion
Primary ciliary dyskinesia	Devices exist to measure the fractional excretion of nitric oxide. There is good data to suggest low nasal NO in the correct clinical scenario (CF has been excluded) is fairly sensitive and specific for PCD. However, despite the fact that this is a very rare disease, a device to test to exclude PCD as a diagnosis could be utilized in many subjects, making the device likely to be utilized far too often for current rare disease diagnostic equipment rules.
Primary hyperoxalosis	More rapid testing to make diagnosis.
Primary immune deficiency	Trec assay in newborn screening.
Primary immunodeficiency diseases	Current techniques for genetic mutation or whole genome sequencing studies to confirm the diagnosis takes 2–6 months. These techniques needs to made some simplified and inexpensive so that these tests can be done in real time and in expedited manner.
Primary ovarian insufficiency (POI)	AMH and natural follicle counts used to dx POI in adults, but modifications and norms needed for adolescents to dx POI. Transvaginal ultrasound to assess POI in adults isn't feasible in teens so better imaging required AMH norms for adolescents also needed
Progressive familial intrahepatic cholestasis	Improves bile transport.
Progressive supranuclear palsy	Ways to measure pathological forms of tau with enough sensitivity and specificity to separate PSP from other causes of symptoms. This could at least separate PSP from Parkinson's disease for example. Possibilities include PET ligands, CSF measurements, serum tests.
Progressive supranuclear palsy	The combination of 7-T structural MRI and Florbetaben (18F) PET imaging could provide a diagnostic test/protocol that would differentiate PSP from clinically similar diseases.
Progressive supranuclear palsy	Neuroimaging but with greater specificity and sensitivity—but will require autopsy confirmation to be convincing. Similarly, CSF or peripheral blood markers could be developed.
Progressive supranuclear palsy	At this time, during life, the diagnosis of PSP remains clinical based on accepted criteria but I feel that these criteria are not sensitive or specific in early PSP. If there were a way to slow progression of this disease, additional diagnostic tests with sensitivity in early PSP are needed.
Prolonged persistent pulmonary hypertension	Genetic bases of this entity.
Pulmonary alveolar proteinosis	Tests for PAP are available as clinical research tests, but they are not available as FDA-approved tests.
Pulmonary alveolar proteinosis	Research diagnostics are available but not in a clinical setting.
Pulmonary alveolar proteinosis	Needs easy access to a blood test to diagnose rather than do a send-out to Cincinnati.
Pulmonary alveolar proteinosis	Need a single specific and widely available diagnostic test.
Pulmonary alveolar proteinosis	Currently a PAS stain on BAL fluid or lung tissue is used to allow an expert pathologist to make this diagnosis. A serum test for PAP would optimally be able to diagnose both autoimmune and occupational disease phenotypes.

Disease Name	Diagnostic Device Suggestion
Pulmonary Alveolar Proteinosis (autoimmune)	ELISA-based GMCSF Ab test (this has been developed but is unavailable for clinical use).
Pulmonary alveolar proteinosis-FDA approved diagnostic anti-GM-CSF assay	This disease is often caused by a circulating antibody to GM-CSF. The test is only available in research laboratories at present. If it were FDA approved, the diagnosis could be made serologically and save people from biopsy.
Pulmonary atresia with VSD and multiple aortopulmonary collateral arteries	Need to better understand the respective rolls of echocardiography, cardiac MRI, and cardiac angiography in determining appropriate surgical approach to this complex, variable heart lesion.
Pulmonary hypertension	Currently, diagnosing pulmonary hypertension may be invasive, requiring catheterization or biopsy; something less invasive would be great.
Pulmonary hypertension	1. Non-invasive way to dx early PHTN before acute crises or ECHOcardiogram changes. 2. Non-invasive method to assess treatment efficacy. 3. Method of better distribution of inhaled therapies. 4. Method to diagnose pulm venous HTN other than cardiac cath or waiting for complications of vasodilator trial.
Pulmonary Langerhans cell histiocytosis	Need a serum/urine biomarker to establish a non-invasive diagnosis.
Pyruvate dehydrogenase deficiency	A std. in vitro biochemical diagnostic test utilizes 14C-pyruvate conversion to 14CO2 to measure residual enzyme activity. A more modern and safer approach would be to standardize the assay using 13C. Hyperpolarized 1-13C pyruvate methodology exists and could be modified into a non-invasive pyruvate—13CO2 breath test to estimate overall enzyme activity, given it's the only enzyme capable of decarboxylating C1 of pyruvate.
Q Fever	Standardization of serologic and or molecular tools.
Rapid diagnostic test for microsporidia keratitis	PCR-based test to evaluate a smear or biopsy. It would be great if speciation could also occur.
Rapid onset dystonia parkinsonism	The only way to diagnosis this now is with screening the gene. There are many mutations. A rapid screen would be helpful.
Rare brain tumors	It is often difficult to tell the extent of the tumor and whether it is growing rapidly.
Rare diseases that are not diagnosed	Consensus on methods for assuring the quality and consistent interpretation of sequencing findings.
Rare genetic malabsorption disorders	We need better genetic screening tests.
Rare kidney stone and mineral metabolism disorders	Better availability of genetic panels to test for monogenic forms of urinary stone disease; also better screening tests to suggest whether or not genetic testing is warranted.
Rare kidney stones	Faster, more specific genetic tests are needed.
Rare tumors, such as chondrosarcoma or minor salivary gland cancers	Well, they are different but the obvious one in salivary gland tumors is a way to screen saliva for cancer, for instance.
Relapsing polychondritis	No diagnostic tests currently exist for RPC. Considering how rare it is, there is apparently no clear interest in promoting research.

Disease Name	Diagnostic Device Suggestion
Renal cancer	Biopsy and pathologic subtyping.
Respiratory disorders related to underlying systemic autoimmune inflammatory disorders: e.g., LIP, NSIP, COP	More novel diagnostic and prognostic biomarkers.
Respiratory failure in the newborn	We need an automatic oxygen adjustment module for this indication and in preemies as well. The nurses are constantly adjusting oxygen and babies are often outside the “therapeutic range”. We need better assessment of oxygen and carbon dioxide levels non-invasively.
Respiratory failure unresponsive to surfactant therapy	Genetic basis of surfactant deficiency would go a long way in our understanding. Currently, these tests are usually “send out” to specific laboratories and there are financial barriers to obtaining them.
Retinal degenerations, such as cone and/or rod dystrophies	There are many types of retinal degenerations, with some not easy to diagnose. The genetic basis of some are understood, but not others.
Retinitis pigmentosa	Many of the genes have been discovered but more in the pipeline that need to be found.
Retinopathy of prematurity (ROP)	1. Infrared indirect ophthalmoscope for comfortable retinal examination for infant. 2. Develop long-working–distance optical coherence–tomography wide-field imaging for easy imaging, without need for examination under anesthesia. Especially older infants who cannot be held steady. 3. Develop wide-field high-speed optical coherence–tomography imaging to identify early peripheral and macular changes of ROP.
Rett and Rett-related disorders	Standardization of genetic testing: sequencing and deletion/duplication need to be offered simultaneously whether ordered as individual test or as a panel. Cost: genetic testing should be offered as part of all insurance, including TriCare.
Rett syndrome	There are genetic tests but they can be difficult to acquire because third-party payers are resistant to pay for the testing. If this could be done in a cheaper and quicker fashion it would benefit this disorder.
Rett syndrome	Need for a mobile device measuring in an integrated fashion respiratory and cardiac/autonomic function including oxygen saturation.
Rohhad syndrome	Efficient genetic testing for ROHHAD.
Sarcoidosis	We need to find an infectious agent, or understand the pathogenesis if the disease is noninfectious, and then base a diagnostic test on the pathogenesis.
Sarcoidosis	There is no single test to confirm diagnosis. A skin test (called Kveim test) using tissue from an affected individual was used in the past but is unavailable at this time due to risk of CJD, HIV etc. A diagnostic test is crucial as at this time sarcoidosis is a diagnosis of exclusion.
Sarcoma	Tests that better predict prognosis and benefits of treatment.
Severe chronic kidney pain in polycystic kidney disease	Catheter-based denervation devices.

Disease Name	Diagnostic Device Suggestion
Severe combined immunodeficiency	Mutational analysis available for all pts not just those with insurance that will pay.
Severe epilepsy of infancy	Quantification of EEG spectra to increase diagnostic specificity.
Sickle cell	Better tests for level of sickle Hg.
Sickle cell anemia	Something to diagnose crisis non-invasively and instantaneously.
Sickle cell disease	Need for bedside test of sickle cell concentration.
Sickle cell disease	Non-invasive imaging of blood flow, in vitro diagnostics for blood cell biophysical properties.
Sickle cell disease	Need better tests to discriminate the presence of a serious infection in febrile patients. Current tests for infection take time, and other lab studies are poorly predictive. Pain assessment in patients with vaso-occlusive crisis is also highly subjective.
Sitosterolemia	High-throughput tandem MS for NBS.
Sjogren syndrome	Need more sensitive biomarkers for Sjogren sydrome.
Sjogren syndrome	A true serological confirmation of the condition.
Skeletal dysplasias	Biomarker test for diagnosis.
SLOS	HT tandem MS for NBS.
Smith-Lemli-Opitz syndrome	Atypical patients are difficult to diagnose. There are methods described to measure enzyme, but they are only available in research labs. The assays for enzyme activity and of tissue sterol analysis need to be adapted for high throughput, relatively simple, reproducible testing.
Soft tissue sarcomas	Using different MRI sequences for improved tumor characterization and better longitudinal follow-up during treatment.
Sphincter of Oddi dysfunction	Probability algorithm.
Spinal muscular atrophy	Newborn screening for early and correct identification.
SSADHD	Solid-state, antibody-based device.
Sticklers	We need a simple way to examine the peripheral retina in a young child without needing to put the infant under general anesthesia. Infrared ophthalmoscopy or wide-field fundus imaging, for example, might allow for an easier examination of the peripheral retina of a toddler.
Sturge-Weber syndrome	Neuroimaging needs to be improved so that its sensitivity in the newborn (or even prenatally) is improved. As it is now, neuroimaging in infants with a facial port-wine birthmark who are at risk for Sturge-Weber brain involvement can miss brain involvement.
Sudden cardiac arrest (SCA)	We are unable to identify causes of SCA in many patients; improved diagnostic testing would help clarify the treatment implications for those patients who suffer from SCA without a clear precipitant.
Surfactant protein deficiencies	Assay for protein or function in respiratory samples.
Syndromic craniosynostosis	Develop a pin-prick blood test to screen for genetic associated syndromic craniosynostosis. This could test for FGFR [fibroblast growth factor receptors]-related abnormalities and provide direction for surgeons and geneticists rapidly.

Disease Name	Diagnostic Device Suggestion
Takayasu's arteritis	MRA, CTA, and PET scan are all utilized for the diagnosis (and sometimes follow-up) of patients with Takayasu's arteritis. However, these studies have limited sensitivity and specificity. Utilization of better imaging qualities or methods may be beneficial.
Takayasu's arteritis—tests to assess disease activity	Using serologic or other biomarkers to create a new measure for Takayasu's arteritis disease activity.
Tardive dyskinesia (TD)	There are subtle movement disorders that could be tested by looking for central motor activity to determine the earliest signs of TD.
The porphyrias	Make the rapid, semi-quantitative test for urinary porphobilinogen generally and rapidly available—especially in emergency rooms, urgent care, etc.
Those at risk for AML (acute myelogenous leukemia)	Detection of "at risk" AML ligands produced by benzene metabolites, such as clinical use of FISH (fluorescent in auto).
Too long to functionally list—but numerous diseases and cancers of substantial rarity	Respondent has encountered disorders in which validation of the test requires national/international access to patients to meet the minimum number of samples for evaluation of performance. Studies can take years. Simply [put]—diagnostics for rare diseases need the same benefits/incentives/protections that treatments do—extended IP protection.
Tourette's syndrome	EEG and fMRI.
Transverse vaginal septum	This diagnosis now typically is delayed until primary amenorrhea is diagnosed at age 14–16, by which time significant pain and potentially damaging retrograde menstruation have already occurred. Current imaging techniques for female pelvis and vagina are limited in ability to visualize these small structures in small children, prior to the damaging effects of obstructed menstruation.
Travel-related pathogens—rare in the U.S., but important for travelers (e.g., Japanese encephalitis virus, Hepatitis E virus)	New test on existing molecular platform.
Triple negative breast cancer	A test to better ascertain prognosis. A test to better predict response to therapies.
TTP	Currently, quantification of ADAMTS13 is key to the correct diagnosis, unfortunately for most facilities this is a send-out test taking 1–2 days to perform a POC test would greatly accelerate arriving at the correct diagnosis.
Tuberous sclerosis complex	Need biomarkers to help determine which TSC lesions are pathologic (propensity to grow or contributing to clinical manifestations) from those that are benign (not contributing to symptoms or propensity to grow).
Type 2 endometrial cancer	Need for earlier diagnosis before metastases.
Unknown diagnosis so need whole exome sequencing	More knowledge about variants of unknown significance.
Urea cycle defects	Needs are for home testing of metabolic status to avoid hospital.
Urea cycle disorders	Home-based ammonia checker. Handheld device for cognitive testing.

Disease Name	Diagnostic Device Suggestion
Urea cycle disorders	Accurate and reliable blood ammonia handheld measuring device for use at the hospital bedside, home. and wherever.
Urea cycle disorders	A home ammonia monitor would be of great use for families to monitor the disease and facilitate early admission or avoid unnecessary admissions to the hospital.
Urea cycle disorders—plasma ammonia	A rapid point of care test for plasma ammonia is needed.
Urea cycle disorders and accurate simple efficient way of measuring ammonia	Under consideration for a home ammonia measuring device, much like a D-stick.
Urine creatine metabolism disorders	Needs to be possible diagnose at birth or even prenatally to ensure optimal treatment. Dietary modification and supplementation can dramatically change developmental outcome.
Uveitides	A test panel that will allow a small fluid sample to be analyzed and adequately diagnose inflammatory conditions, similar to PCR for infections.
Variety of pediatric oncology disorders	Again, per my comments about SCD, what is needed are better tests that help to discriminate children (e.g., fever and neutropenia) with serious infections from those who are not infected. This would allow better stewardship of antimicrobial agents, reduction of microbial resistance, less hospital admits.
Very long chain acyl coA dehydrogenase deficiency	VLCAD is often suspected after newborn screening. The challenge is proving whether or not the patients are actually affected. What's needed is a method for measuring VLCAD enzyme in blood. Such a test exists, but is not sensitive, specific or accurate enough. It needs to be modified, improved.
Viral infections of the CNS, particularly in immune suppressed patients	Pathogen discovery would include deep sequencing of RNA and or DNA from CSF and appropriate bioinformatics to diagnose the infection.
VLCAD deficiency for diagnosis	The diagnosis of this condition can be difficult to accomplish. Even genetic testing can be insufficient because if a single allele is ascertained it doesn't prove that they individual is a carrier as opposed to an affected person with a second un-ascertained pathogenic variant. There is a good enzyme test, and the current "gold standard" of measuring labeled fatty acid oxidation and fibroblasts can leave ambiguous results.
Von Hippel-Lindau	Quicker sequencing.
Wiskott Aldrich syndrome—newborn screening	Would probably have to be measuring amount of WAS protein in blood, something that is not currently done. Currently, look at WASp expression on lymphocytes by flow cytometry.
X-linked retinitis pigmentosa	I don't know how to do this, National Eye Institute (NEI) Study Section turned my grant to glaucoma a decade ago for the public health focus. My suggestion is that the FDA pushes NEI to valorize study of x-linked RP and other "minor" eye diseases. If I had been funded for RP research, as well as glaucoma, by now, I could tell you how to create a device or test, but NEI's Study Section drove me away from studying RP.

APPENDIX F: THERAPEUTIC DEVICE SUGGESTIONS FOR SPECIFIED RARE DISEASES

Disease Name	Therapeutic Device Suggestion
Acanthamoeba keratitis	Some sort of in-office clinical assay to diagnose AK (tear test).
Active tuberculosis (TB) developing from latent infection	Pathogen-specific detection of latent TB infection is needed so treatment can be initiated before disease develops.
Acute cardiopulmonary failure in children (necessitating mechanical support like ECMO/VAD/etc.)	ECMO and ventricular assist devices are the most common mechanical means of support for decompensated heart failure in children. With respect to ECMO, all use is off label, and ECMO devices are different from center to center. There exists a need to develop a "best-of-breed" ECMO circuit, using data from the ELSO Registry and similar other data sources, that would reduce ECMO-related complications, allow improved comparability of outcomes between centers, and ultimately hopefully improve survival.
Acute intermittent porphyria (and other acute porphyrias)	A device for rapid testing for porphobilinogen would be a major advance.
Acute kidney injury	There are no pediatric specific catheters or devices that are designed for the smallest pediatric patients.
Acute renal failure in children	Modification of existing Foley catheters with sensors to detect acute kidney injury biomarkers.
Airway support in children (dissolving stents for the trachea)	An unstable airway remains challenging.
Alagille syndrome	Prevent the loss of bile ducts.
Alpha-1 antitrypsin	More affordable method of replacement; may include repurposing of current development.
Alpha-1 antitrypsin	Improved oxygen delivery.
Alpha-1 antitrypsin deficiency	The Alpha-1 antitrypsin deficiency population has been excluded from almost every current study for bronchoscopic lung volume reduction for advanced emphysema with hyperinflation. This is not the FDA's fault, but sufficient incentives to advance device work in the rare disease space are limited by companies holding out for Medicare's new technology add-on codes ($$) that enhance revenue for new devices on the basis of volume (e.g., with common diseases) instead of innovation.
Alpha-1 antitrypsin deficiency (liver disease)	There is no treatment for the liver disease. Looking for a treatment to correct the aberrant protein.
ALS	Need fundamental, disease-altering Rx that has a major impact on disease progression.
Alternating hemiplegia of childhood	These children have mutation in ATP1A3, which affects neuronal firing. A new device would re-set the firing rate before there is cell death. Cell death was seen in elderly brains that we studied.
Amyotrophic lateral sclerosis	More efficient computer based alternative communication devices are needed, as are more compact power mobility devices and more effective and comfortable interfaces for non-invasive respiratory equipment.
Amyotrophic lateral sclerosis	There is no way to diagnose until later onset. Novel blood test, imaging, or other nerve tests needed.

Disease Name	Therapeutic Device Suggestion
Amyotrophic lateral sclerosis (Lou Gehrig's disease)	A device that can restore the function of neurons affected or to stop the progression of the disease.
Anaplastic thyroid cancer	Non-surgical treatment.
ANCA associated vasculitis	Need app to help direct therapy based on specific type of vasculitis and features.
Aniridia	A supra choroidal stent is in development but not yet FDA-approved. It would be excellent for this disease because it would not destroy their few stem cells and this is a glaucoma refractory to traditional treatment. There is also an artificial iris that is not FDA-approved that would be safe and useful and life changing.
Aniridia	Need limball stem cell treatments—ability to repopulate stem cells.
Anterior chest wall deficiency syndromes	Need a device that can bridge transversely the anterior thorax that can be used as an attachment structure for the vertically placed VEPTRs.
ARPKD	Better treatment options to prevent progression.
Arterial stenosis	We need biodegradable stents to treat pulmonary or aortic stenosis.
Atrial septal defect	Catheter-delivered, biodegradable closure device.
Atypical hemolytic uremic syndrome (aHUS)	We need better concentrates of complement components to treat this disease.
Autoimmune encephalitis (e.g., antiNMDAR Ab)	Something more specific for the Ab other than routine anti-inflammatory Rx.
Autoimmune Pulmonary Alveolar Proteinosis	Inhaled GM-CSF has been demonstrated to be effective in 62–95% of patients with autoimmune PAP. We are engaged in attempts to conducts safety studies (first) and pivotal studies (subsequently) in order to improve our understanding of the dosing and administration of inhaled GMCSF therapy of autoimmune PAP. This will require the use of a high efficiency nebulizer system.
Autoimmune pulmonary alveolar proteinosis	GM-CSF inhalation.
Avascular necrosis	A new technique to allow for preservation of bone.
Biodegradable scaffolds for congenital heart disease patients	Biodegradable scaffolds are available for the treatment of coronary artery disease. If this technology could be modified for use in patients with congenital heart disease in terms of sizes and delivery systems, it could be a paradigm shift in the management of many patients with congenital heart disease.
Birt-Hogg-Dubé disease	More specific genetic test that is highly predictive of disease.
Bladder pain syndromes	Some intravesical method to change bladder sensation.
Bone cancers (osteosarcoma, lymphoma)	Non-invasive ablation of tumor cells without chemo or radiation. Avoid amputation or wide excisions.
Bone sarcomas	More robust orthopedic implants and improved techniques for bone graft to reduce hardware and/or graft failures for limb preservation surgery.
Brain AVM	We really need devices currently C-marked which are available in Europe but are not available in the U.S., or we need manufactures in the U.S. to build devices equal to or superior in performance to what is available in other parts of the world. U.S. available devices are currently 3–5 years behind.

Disease Name	Therapeutic Device Suggestion
Brainstem tumors (DIPG)	Development of indwelling catheters with access ports to allow direct drug delivery to brain tumors, particularly in the brainstem.
C3 Glomerulopathy	New therapies that target different stages of complement cascade activation are needed.
Cancer	Less chemotherapy methods, and some oral and herbal methods.
Cardiac structural deficiencies (e.g., HLHS)	Need a Tissue Engineered Regenerative solution for adding structural and functioning muscle to hearts (i.e., TERM applications of personalized or precision medicine).
Carniofacial abnormalities	Development of a molecular signal jamming therapeutic to be injected into the prematurely fusing cranial sutures to counteract the dominant gain of function mutations.
Catatonia	Maybe you could repurpose and ECT device or maybe you need a new device to treat the catatonia.
CDKL5 encephalopathy	There is no effective treatment for the severe epilepsy that accompanies this condition.
Central apnea in newborns	Need better ways to stimulate the diaphragm.
Cerebral vasospasm	Smaller diameter balloon angioplasty device with smaller tip to permit improved access, performance, and safety.
Cervical dystonia	Although DBS may improve patients with cervical dystonia, it is invasive, cumbersome, and does not provide consistent relief. Preferable would be the development of a non-invasive device (TMS for example) that could be modified to be clinically useful.
Charcot-Marie-Tooth disease	Increasing data sharing of genetic causes of Charcot-Marie-Tooth disease and working to make testing more available and affordable.
Charcot-Marie-Tooth disease	AFOs effectively treat many of the limitations associated with CMT. Patients struggle with these at times. Improved AFO construction would improve quality of life.
Charcot-Marie-Tooth disease	Many CMT patients would benefit from an AFO (ankle foot orthotic) that enhanced walking. The chief limitations from current AFOs are the foot deformities that make such devices painful to wear, and the underutilization of devices that “store” energy to enable gait (a feature of normal gait). The military has invested in such devices for amputees but this technology has not been transferred to the needs of CMT patients.
Charcot-Marie-Tooth disease	Better assistive mobility devices.
Chronic graft-versus-host disease	Therapies that are approved for other indications are often tested for cGVHD.
Chronic graft-versus-host disease	Devices to improve patient function.
Chronic granulomatous disease	Ablation of refractory infections.
Chronic total occlusion of a coronary	A safer and faster way to cross coronary occlusions.
Colon cancer	New chemotherapy.

Disease Name	Therapeutic Device Suggestion
Combined immunodeficiencies	As genetic understanding continues to improve, gene therapy or enzyme replacement would be ideal ways of promoting these. Currently, our treatment is only supportive unless severe enough to warrant a bone marrow transplant.
Congenital cardiac valve disease	Need regenerative Tissue Engineered valves that can grow with the child and sustain matrix remodeling life-long thus obviating multiple re-replacements.
Congenital diaphragmatic hernia	Need paracorporeal lung device to support extrauterine gas exchange immediately after birth and permit reduction in pulmonary vascular resistance.
Congenital diaphragmatic hernia	Closure devices for large diaphragmatic defects.
Congenital diaphragmatic hernia	Children with congenital diaphragmatic hernia suffer from pulmonary hypertension and acquire lung damage even from our gentle ventilation strategies. The ability to provide less traumatic ventilation and more targeted treatments for pulmonary hypertension could relieve much of their ongoing dysfunction.
Congenital dilated cardiomyopathy	Decrease size of available ICDs for pediatric use.
Congenital disorders of glycosylation	We need better therapeutic approaches since at the moment very few subtypes can be treated. Mannose supplementation can be provided for PMI-CDG.
Congenital glaucoma	Like the treatment of Aniridia, congenital glaucoma is difficult to treat and we don't have a suprachoroidal stent to treat it when the other, more [conventional] treatments have failed. The only option when all other things have failed is a destructive procedure.
Congenital heart disease	Absorbable vascular stents, various absorbable and nonabsorbable occlude devices, catheter delivery systems.
Congenital heart disease associated with aortic coarctation of aorta or pulmonary artery stenosis	Bioresorbable stents specifically for young children, infants, and neonates.
Congenital heart disease patient require better mechanical circulatory support	Adaptation of LVADs for support of Fontan patients with heart failure, miniaturization of VADs.
Congenital hydrocephalus	Novel materials for shunt manufacture, and integrated ICP sensing using transcutaneous tools.
Congenital micrognathia with airway obstruction	Self-contained mandibular distractor with internal timer/advancement or other way to activate (wand/smart chip wave over area?).
Congenital peripheral pulmonary artery stenosis	Catheter deliverable vascular growth factor.
Congenitally inherited inborn errors of metabolism/acid oxidation defects	New device for testing; or perhaps, new tests that can be processed on available machines.
Corneal dystrophies	Likely, we are speaking about drug to bind dystrophic material or genetic intervention to prevent accumulation of dystrophic material, rather than a device.

Disease Name	Therapeutic Device Suggestion
Corneal ectasia (postrefractive surgery, keratoconus, pellucid marginal degeneration)	A UV-light delivery system for collagen crosslinking. The device exists but getting FDA approval has taken an inordinate amount of time.
Corneal stromal and anterior basement membrane dystrophies	Currently, there is only one FDA-approved device that can treat corneal stromal and anterior basement membrane diseases using PTK (Photo Therapeutic Keratectomy). This limits treatment of these conditions to centers that only have this laser model, yet there are [at] least four other excimer laser brands approved for LASIK, which could also treat these conditions and do internationally, but it is too expensive and burdensome for the companies to seek approval for this orphan group of patients. Internationally, all of the current generation of excimer lasers are treating these conditions which have been treated successfully for 20 years, both in the U.S. and internationally. A paper PMA or 510K-type approval or alternative should be considered for the other excimer laser models, which are already approved for LASIK in the U.S.
Corticobasal degeneration	A drug or device that could alter the pathogenic mechanisms of this condition.
Cowden syndrome	PTEN-informed high risk surveillance or prophylactic surgery is standard of care for Cowden syndrome. But that is a lot of organs to surveillance each year! We need a safe preventative, perhaps a polyvalent vaccine?
Craniosynostosis	Intervention at an earlier period to prevent bone growth and fusion.
Crohn's arthritis	Comparative studies to determine the best form (material, etc.) for implants.
Crohn's disease	Suspect the microbiome (fecal microbes) may play major role in initiation of disease activity. Ideally, better understanding of interaction between mucosa/inflammatory system and fecal microbes will be important in developing alternative therapeutic strategies.
Cystic fibrosis	For the mother, it would be a home device for monitoring her complications or the status of her CF—primarily digestive and respiratory. For the fetus, it would be about therapy to reduce complications to the fetal GI tract and, potentially, the respiratory tract.
Cystic fibrosis	A therapy that can modify the underlying genetic mutation of this disease.
Cystic fibrosis	Again—what's out there isn't bad. But it currently takes a lot of time and effort it takes for patients to do their airway clearance therapy.
Cystic fibrosis	Gene modification and artificial lung technology.
Cystic fibrosis	Must fix the underlying problem.
Cystic fibrosis	Some form of genetic alteration/gene therapy to restore the normal physiology.
Cystic fibrosis	Thinking more of drugs than therapeutic devices. But it is going to be exceedingly difficult to study and get approval for drugs in CF patients with rare mutations. There are not enough with rare mutations to perform large enough phase 2 or 3 clinical trials. We need to be able to rely upon biomarkers, maybe on an individual level, to get approval of drugs for CF individuals with rare mutations.
Cystic fibrosis	New devices or device modification could address a multitude of areas, such as mucus clearance, nutritional improvement, pancreatic replacement.

Disease Name	Therapeutic Device Suggestion
Cystic fibrosis	Improved devices to deliver drugs to alveoli to address local issues, better topical antibiotic or gene therapy delivery.
Cystic fibrosis (many different mutations)	Not a device but more therapeutic agents.
Cystinosis	Newborn screening on blood samples and more rapid diagnosis on patients during follow up visits to clinics.
Dent disease	More research needs to be done.
Desmoid	Device similar to radiofrequency ablation in solid organs, only here challenge is neighboring blood vessels of small bowel mesentery.
Desmoid tumors	MR- or US-guided ablation of desmoid tumors. Need to identify critical structures better.
Device for closure of perimembranous VSD	Several devices are available worldwide that have successfully been used to close perimembranous VSDs (none are available in the U.S.).
Device for closure of preemie PDA	There is currently a device manufactured by St Jude that is designed for use in the premier PDA. It is not available in the U.S.
Duchenne muscular dystrophy	Biomarkers discovery and following development of a therapeutic chip for patient stratification for trials and treatment.
Duchenne muscular dystrophy	Total artificial heart for cardiac involvement.
DVT/PE in children	Need smaller filter devices for smaller vena cavas.
Dyskeratosis congenita	Develop novel gene correction strategies for multiple cell types, i.e., hematopoietic stem cells, skin stem cells, pulmonary and liver cells.
Dystonia	Dystonia patients who receive deep brain stimulation under an HDE are not approved to receive rechargeable technology which would obviate frequent battery pacemaker changes. The company (Medtronic) does not want to incur the costs to change the labeling, even though rechargeable technology is standard of care for FDA DBS uses (i.e., PD and ET).
Dystonia	The pathophysiology is presumably d/t cortical/subcortical abnormalities. Developing therapies targeting that region would be important.
Dystonia	Deep brain stimulation. It is only FDA-approved for “primary” dystonia in USA. This limits is use for “non-primary” dystonias.
Dystonia	Currently we treat generalized dystonia, especially genetic forms, with deep brain stimulation. The benefit is not always clear. Need refined DBS techniques with novel programming techniques, refined electrodes, and possibly other sites in the brain to stimulate.
Early accurate intrauterine diagnosis of congenital heart disease & treatment	Higher resolution.
Early onset scoliosis	Smaller and more reliable spine implants that lengthen the spine without surgery.
Early onset scoliosis	Need better spinal fixation devices for EOS.
Ebstein’s anomaly	Perhaps new annuloplasty device, valve repair device, valve replacement.
Ebstein’s anomaly	Novel surgical approaches applied to appropriate patient subsets.
Ehlers-Danlos disease	Mechanisms to improve hemostasis for this disorder.

Disease Name	Therapeutic Device Suggestion
Emerging or re-emerging pathogens (e.g., adenovirus type 14)	Prompt and accurate diagnosis of an Ad14 infection would facilitate treatment with appropriate antiviral drugs that have demonstrated clinical efficacy for adenoviruses.
Eosinophilic colitis	Potentially topical or swallowed steroids, and/or monoclonal antibodies.
Eosinophilic esophagitis	Endoflip is currently being developed as a tool to quantify esophageal compliance. Whether it truly correlates with disease activity in EoE (as measured by PROs and or other measures of disease activity) is still unknown.
Eosinophilic esophagitis	Uncertain if device is needed, but eosinophilic esophagitis specific treatment modalities are needed.
Eosinophilic esophagitis	Topical acting corticosteroids used normally for asthma.
Eosinophilic esophagitis	This would be an instrument to deliver topical therapy to the esophagus.
Eosinophilic esophagitis	Swallowed corticosteroids are effective in most patients but are not approved to treat EoE.
Eosinophilic esophagitis	Non-invasive saliva-based test.
Eosinophilic esophagitis	Medication delivered to target organ with minimizing side effects (e.g., fluticasone).
Eosinophilic esophagitis	Improve dilation.
Eosinophilic esophagitis	Enterotest.
Eosinophilic esophagitis and eosinophilic gastrointestinal disorders (in general)	A device that would allow for evaluation of dysmotility in the esophagus.
Eosinophilic gastritis	Swallowed steroids may be helpful but alternative therapies such as monoclonal antibodies may be important.
Eosinophilic gastrointestinal disorders (EGID)	Adaptation of topical steroids, such as those used in asthma, for better administration to the esophagus, as well as a way to allow these medications to penetrate other parts of the intestinal tract.
Eosinophilic GI disease	Non-diet and non-steroidal therapies safe for children and adults.
Eosinophilic granulomatosis with polyangiitis (Churg Strauss)	This is a very rare disease and large prospective studies on new drugs are difficult to do. New drugs would be a major advancement in the field.
Esophageal adenocarcinoma	We need improved nonsurgical methods of treating this cancer and precancerous forms of the disease.
Esophageal atresia	Our current treatment involves several operations. A less traumatic device, perhaps magnetic, to approximate the two ends would help.
Failing and dysfunctional single ventricle physiology	External compression device for at-home use; intravenous blood pump for circulatory support— long-term and short-term
Familial depression	Deep brain stimulation doesn't need new device but application of current device to the issue. Needed research.
Familial LCAT deficiency	Enzyme replacement therapy is needed.
Familial spastic paraplegia	Drug available, unavailable secondary to cost.

Disease Name	Therapeutic Device Suggestion
Fatal diseases in infancy with mutated protein product	Implantable device that would allow cells to survive that would produce the missing normal protein continuously over long periods of time.
Focal dystonia	I am thinking only short term here. Modifying noninvasive brain stimulation devices might be helpful.
Focal segmental glomerulonephritis	There is only nonspecific treatment at this time.
Focal segmental glomerulosclerosis	The current therapy is already repurposing treatments from other diseases. There has been no convincing therapy for this condition, and no breakthrough has occurred for this disease in the last 3–4 decades.
For a number of uncommon diseases, apheresis is the treatment of choice. Getting new apheresis machines approved for all the indications has been very slow.	We use apheresis to treat antibody mediated disease because it works well for myasthenia gravis, Guillian-Barré, and a few other well-described uncommon conditions. We need to use it for Wilson's disease (10 patients in the national registry), but getting an IND and conducting a trial is difficult. Please figure out a mechanism to conditionally approve the machines for rare indications.
Gastroparesis	New device to stimulate gastric nerves or muscle to result in restored peristalsis.
Generalized dystonia	DBS is the standard medical device used for generalized dystonia. However, issues regarding complications, long-term efficacy, need for adjustments, and battery life are all relevant.
Genetic diagnoses of primary immunodeficiency disorders	In the treatment of immune reconstitution of PIDD, there are unmet needs identifying best stem cell source, conditioning, post-transplant GVHD therapy. Gene therapy needs expansion.
Genetic disorders of surfactant metabolism in newborn infants	Paracorporeal lung device to support lung function.
Genetic testing identification	A function of what disease it would identify.
Giant cell arteritis	Currently, long-term glucocorticoids are the only proven therapy for giant cell arteritis. Many times patients have multiple side effects with the glucocorticoids. New medications are needed to help patient get off glucocorticoids sooner.
Glycogen storage disorder type 1a/1b	A device for continuous glucose monitoring that is sensitive to low blood sugars and that can alarm parents when patients are nearing a low range. Also, could have alarm that alarms for corn starch/glycosade dose times.
Graft-versus-host disease after allogeneic hematopoietic cell transplantation	Immunosuppressive/modifying medications for other conditions (solid organ transplant, etc.) may be useful for treatment of GVHD after allogeneic hematopoietic cell transplantation.
Granular corneal dystrophy	Gene therapy for this corneal disease.
HD	ASO will require a pump to administer the treatment, other treatments may require pump for brain. DBS could be repurposed if found helpful, onset of manifest disease could be developed with sensitive behavioral tests or a biomarker of brain disease—both would markedly advance the field.
Heart failure in small children	Currently only one support (VAD—Berlin Heart) is appropriate for use in small children. Miniaturization and development of more easily managed devices would have a significant impact for this population.

Disease Name	Therapeutic Device Suggestion
Heart failure with preserved ejection fraction	Total artificial heart.
Hemophilia	Tests for factor levels.
Hemophilia	An implanted device that would provide antihemophillic factors in useful amounts for long periods of time.
Hereditary pancreatitis	It would have to be gene replacement therapy.
Hereditary retinopathy	Stem cell, genetic modification.
Heritable pulmonary arterial hypertension	Need portable oxygen concentrators to deliver higher O2 flows with activity.
Heterotopic ossification of wounds	Depending upon the application, a combination of negative pressure wound dressing and chelating healing agents might be more effective in removing the HO at superficial levels. For deeper tissue levels, additional investigations are required.
HHT	There are many anti-angiogenic drugs that are available that can be used. Pre-clinical models of HHT 1 and HHT 2 are available. A proof of concept study would need to be performed in these animals to see if the drug reduces progression of HHT. In addition, one could use ELISA to measure angiogenic cytokines in patients who are symptomatic such as epistaxis. The ELISA would include know angiogenic cytokines such as PDGF, VEGF-A, TGF-B, FGF-1, PLGF, MMPs, and others. Based on the ELSIA, the appropriate anti-angiogenic drug could be used, which decreases [the] elevated levels. And reduces the epistaxis. If one could identify imaging markers for these cytokines, than patients could potentially be screened using imaging.
Huntington's disease	Physical and occupational therapy techniques and devices are understudied in HD. Deep brain stimulation may be modified for HD. Cognitive symptoms are a major unmet need, but can be tractable to intensive programs, such as mindfulness training or CBT web- or device-based training/interventions, could enable patients and caregivers to do daily programs with symptomatic and functional relief without interacting with a care provider every session.
Huntington's chorea	Effective, noninvasive, inexpensive.
Huntington's disease	Patients with HD have severe disabling movement control disorder. Device like DBS with neuroimaging and electrophysiological targeting may help to alleviate these symptoms.
Huntington's disease	Investigate deep brain stimulation in Huntington's to treat the chorea.
Hyperammonemia	Ammonia removal is only partially accomplished with hemodialysis. Modification of the filtration system could allow for selective removal of ammonia and other toxic hepatic metabolites.
Hyperammonemia in urea cycle disorders—for monitoring and care	A device that could reliably measure blood ammonia for families of urea cycle disorder patients could facilitate early treatment and comprehensive management of these complex conditions.
Hypersensitivity pneumonitis	Improvement on existing use of prednisone and other immune suppressants.
Hypersensitivity pneumonitis	Better therapy.

Disease Name	Therapeutic Device Suggestion
Hypertrophic obstructive cardiomyopathy	A device that anchors the occlusive balloon in a septal perforator artery with varying sizes to accommodate varying vessel sizes.
Hypoplastic left heart syndrome	Use of mechanical support for cardiomyopathy; develop a system that would balance qp/qs; decrease trauma to blood elements.
Hypoplastic left heart syndrome	Although mortality has improved over the past 3 decades, there is still significant post-operative and inter-stage mortality after Stage 1 palliation that warrants advancements in surgical techniques (and non-surgical interventional alternatives) and improved home monitoring.
Icthyosis	We need better car seats and positioning devices to meet the needs of these patients
Identification of anomalous origin of a coronary artery, and its impact on sudden death	Need very high-resolution echo that could be used for accurate screening for anomalous coronaries, coupled with a follow-up program to see what the best therapy might be, and when it should be implemented.
Idiopathic emesis	It would be helpful if the cause of idiopathic emesis could be identified which, being idiopathic, makes it hard to know where to begin.
Idiopathic intracranial hypertension	Because the underlying physiology is not well understood, the exact nature of a breakthrough device is unknown.
Idiopathic pulmonary fibrosis	Need to better understand the reason for the disease and its rate of interstitial scar progression. Progression varies according to the type of fibrosis and the underlying condition of the patient. A lung transplant is not always possible. The mechanism of scar tissue spread between lung lobes is unknown and surgical resection by lobectomy is not practical. Drugs are not yet effective in slowing, stopping or preventing the disease. Continued drug research to stop or reverse scar tissue by new tissue growth is perhaps still the major mystery.
Idiopathic pulmonary fibrosis	Oxygen delivery systems are inadequate, inconvenient, intrusive. We need oxygen delivery systems that are lightweight, unobtrusive, long-lasting, and have zero out-of-pocket cost to patients.
Idiopathic pulmonary fibrosis	Need medications that stop progression of IPF.
Idiopathic pulmonary fibrosis	Nasal high-flow therapy
Idiopathic retroperitoneal fibrosis	Most people with IRF require ureteral stents or percutaneous nephrostomy tubes. Could the tubes, which are close to the site of disease, also be tooled for drug delivery/therapy?
Imperforate anus	Incontinence and constipation are frequent problems in children who have undergone an operation for imperforate anus. An image-guided device to locate the center of the internal anal sphincter and approximate it to the optimal location in the external anal sphincter without having to disrupt pelvic anatomy should improve function.
Implantable artificial organs	Heart, lung, kidney, liver.
Inborn errors of metabolism	A device or biological system which will be able to remove ammonia from the blood which is not as invasive as dialysis and can be used in many medical facilities even at home.

Disease Name	Therapeutic Device Suggestion
Infantile spasms	Need a better understanding of the cause.
Inflammatory breast cancer (IBC)	Difficult as IBC does not have a unique molecular signature, distinct from other breast cancers.
Inherited retinal dystrophies	Effective gene replacement therapy is needed.
Internal carotid artery aneurysms warranting parent vessel sacrifice	Detachable balloons were an excellent and economical means to achieve this end but none are presently approved for use in the U.S.A. Other methods to achieve this end exist and are typically used in an off-label fashion, often at a considerable cost. An endovascularly deployable covered stent graft with assured proximal and distal wall adhesion would be an option to preserve the parent vessel in some cases in which the vessel would otherwise be sacrificed; however, no such device exists.
Internal carotid artery dissection with associated symptomatic stenosis (ICA)	Stents approved for use in the cervical ICA are meant to be used as a treatment of ICA stenosis due to atherosclerotic plaque which tends to be stiff, not readily deformable, and located in the proximal ICA: stents for that purpose are therefore substantial and tend to be relatively inflexible. Dissection associated stenosis are deformable, without stiff calculations, in the distal cervical ICA, may extend into the skull base, and require a neuroform-type stint.
Interstitial lung diseases	Device to improve gas exchange in patients with respiratory insufficiency.
Irregular corneal astigmatism	Corneal topography driven Photo Refractive Keratectomy (PRK) can be used to reshape corneas to make them more regular by removing a minimal amount of tissue yet regularizing their corneas, so they can be corrected with improved visual quality with either glasses or contact lenses. This is being done internationally and I have had over 30 patients I have referred to Canada for treatment who have returned with excellent results.
Isolated, idiopathic dystonia	Several different approaches could be reasonable: improved targeting and understanding of deep brain stimulation for symptomatic relief that may vary depending upon part of body affected by dystonia; new drugs to alter pathogenic mechanisms in the brain or better symptomatic treatment with either improved chemodenervation or oral medications.
Jarcho-Levin	Direct lengthening device for the thoracic spine, additional capability of widening the rib cage.
Jeune	Current standard of care VEPTR. Need new device that expands base of thorax also and segmentally lengthens each rib, with mobilization of costal-vertebral joints to allow rib cage expansion with inspiration.
Keratoconus	Corneal UV Cross linking is available worldwide for the past decade and yet not available in the U.S. because of the difficulty funding and performing an FDA device study. The treatment also requires the use of dilute riboflavin, which further complicates the approval process since the drugs group needs to also evaluate the treatment.
Keratoconus	Cross-linking and contact lenses.
Keratoglobus	Corneal cross-linking using riboflavin and UV light is readily available in Europe, but remains unavailable for patients in the U.S.

Disease Name	Therapeutic Device Suggestion
Kernicterus	Deep brain stimulators have been used with some success but there are no studies documenting efficacy or indicating in which are of the brain the device should be placed.
Kleine-Levin syndrome	Kleine-Levin syndrome (KLS) is characterized by a marked suppression of slow sleep (N3 sleep). Transcranial magnetic stimulation (approved by the FDA for depression) leads to robust enhancement of slow wave sleep. Clinical trials are needed to assess if TMS will also improve KLS.
Krabbe disease	Something that would easily monitor biomarkers in blood.
LAM	Specific drug and respiratory device.
LAM	Medications, management of pulmonary complications, chylothorax.
Large congenital nevus	Creation of in vitro skin and dermal layers derived from patients that can be used to provide coverage of large areas where suspicion for malignancy requires surgical excision.
Large thermal burns 60% TBSA	We need a total skin replacement, both of epidermal and dermal elements. Ideally, this would not require a long time to culture in the lab while waiting for the skin cells to grow.
Larsen's syndrome	A drug to alter the collagen abnormalities.
Laryngeal dystonia	Something more disease centric—not symptom centric.
LCAT deficiency	There is a need for enzyme replacement therapy.
Leber's congenital amaurosis and other rare optic neuropathies	In the absence of a truly effective therapy for this condition, most approaches to "therapy" are rehabilitative. As such, effective and practical vision rehabilitation methods and devices are needed.
Lennox-Gastaut syndrome (LGS)	There are a number of neuromodulation approaches to treatment of LGS in the literature, including external trigeminal nerve stimulation and thalamic nerve stimulation that merit study.
Lesch-Nyhan disease	Deep brain stimulation works for LND. However, insurers will not cover it because they label it as experimental since it is not specifically FDA-approved for LND.
Leucoencephalopathies	Ability to deliver therapeutic agents to the brainstem.
Leukodystrophies with the exception of adrenoleukodystrophies	Educating physicians to properly read brain MRIs. Designing new molecular tools for rapid and low-cost diagnosis.
Limb ischemia without surgical or percutaneous options	Stem cell therapy.
Lipoatrophic diabetes	Leptin deficiency relates to lipoatrophic DM. Usually meteleptin given as SQ Bid or QD. Limited help. Try leptin delivery by insulin-like pump.
Lipodystrophy	Need the diagnosis and treatment are very specific.
Lipomyelomeningocele	Secondary tethering of the spinal cord after initial surgery for repair and untethering of lipomyelomeningocele is a significant problem for which no implant or technique has demonstrated any efficacy in preventing.
Long gap esophageal atresia	Lengthening devices.

Disease Name	Therapeutic Device Suggestion
Long QT syndrome	Right stellate ganglion stimulator to shorten QT interval.
Long QT syndrome (LQTS)	Similar to needs in unexplained SCA, some patients with LQTS are quite young, and so the risks associated with ICD implantation are not balanced by associated benefits. Less risky devices in regard to implantation and complications are needed for this population.
Lung failure in newborn and children	Implantable lung.
Lymphagioleiomyomatosis	There are several preliminary studies suggesting that drugs for other disease may be useful in treating LAM (statins, hydroxycholoroquine, doxycycline, etc.); testing these in combination with the FDA approved therapy of sirolimus may be helpful.
Lymphangioleiomyomatosis	We need something to cure LAM, not just suppress its progression.
Lymphangioleiomyomatosis	Some of the bronchoscopic lung volume reduction devices may work well for advance LAM.
Lymphangioleiomyomatosis	Perhaps immunotherapies as used in cancers.
Lymphangioleiomyomatosis	Need portable oxygen concentrators to deliver higher O2 flows with activity and associated forehead probe oximeter to monitor SpO2.
Lymphangioleiomyomatosis	Improvements in lymphagic imaging, improvements in therapeutic medication delivery systems.
Lymphangioleiomyomatosis	I have no specific suggestion but chemotherapy for CURE would be very helpful.
Lymphangioleiomyomatosis	Better cytotoxic drugs for LAM.
Lymphangioleiomyomatosis	Anti-estrogen therapy.
Lymphangioleiomyomatosis—FDA-approved diagnostic VEGF-D assay	The VEGF-D biomarker also appears to have prognostic and predictive value
Lymphangiomatosis	If the concentration of serum VEGF-D drops after treatment, we consider the therapy of LAM is effective.
Lymphangiomyomatosis	Improved oxygen delivery.
Lynch syndrome	Eradicated DNA mismatch repair deficient cells.
Lysosomal storage diseases	New therapies, particularly targeting CNS disease.
Mal de débarquement syndrome	A device designed to cause a resetting of the vestibular processing of information back to prior to the shift occurring following sea travel.
Many tropical infections (e.g., loa loa)	Current treatment of filarial diseases is burdensome; the drugs are fairly toxic.
Mastocytosis/mast cell activation syndrome	A treatment that truly stabilizes mast cells is needed.
MECP2 duplication disorder	For the same reason, a much simplified platform to initiate communication and to assess intellectual level would be greatly beneficial.
Medullary thyroid cancer	Better nonsurgical therapy.

Disease Name	Therapeutic Device Suggestion
Melanoma	Imaging technology with specificity for nodal metastases, genetic test that predicts prognosis and likelihood of treatment failure with surgery alone.
Membranous ventricular septal defects	Adjust shape and flexibility of existing occludes.
Metastatic disease to the spine	Radioactive bone cement for kyphoplasty of the spine for metastatic disease.
Mitochondrial disease	There are lots of drugs that likely would help mito disease patients, if could characterize their greatest degree of dysfunction and response to therapeutic candidates.
Mitochondrial disorders	We need better designed clinical trials since currently there are no therapeutic options.
Mitochondrial disorders	There is not a single FDA-approved drug for treatment of mitochondrial disease. Repurposing might be possible, but novel therapeutics seem more likely to have an effect.
Mitochondrial disorders	New therapeutic devices should be developed to treat the neurological symptoms of mitochondrial disorders. These devices would also have benefit for other rare neurological diseases.
Moderate and severe pediatric traumatic brain injury	Children at different stages of development have acute care needs as well as rehabilitative needs and strategies that differ from adults. There are a number of things that fall into this category, as TBI comes in various forms.
More transcatheter valve options for congenital patients (smaller sizes)	Need smaller transcatheter valve options for valve in valve replacement, but also native valve replacement. Not just pulmonary, but mitral and aortic, as well.
Most retinal degenerative diseases (e.g., Stargardts)	No suggestions. Therapy is essentially lacking for most types of retinal degenerations, leading to blindness. Therapeutic options or devices are lacking. Gene-based therapies would appear the most promising.
Mucopolysaccharidoses	Develop enzymatic or genetic modification to alter the disease metabolism.
Mucopolysaccharidoses (newborn screen)	Creating new tests using the current newborn screening blood cards.
Mucus membrane pemphigoid	Surgical repair of ocular surface that doesn't exacerbate disease.
Multiple forms of dwarfism	As an academic total joint surgeon, I often encounter patients who are so small that existing joint implants cannot be found due to size.
Multiple myeloma	A device that can cure this curable disease.
Multiple myeloma	Current therapy is woefully inadequate—5-year survival remains too low.
Multiple myeloma	Device to treat plasmacytomas or minimal residual disease (MRD).
Multiple myeloma	I am a surgeon. Surgical treatment of multiple myeloma is palliative and relatively unsatisfying.
Multiple myeloma	Work on new chemo therapeutic and immunological approaches.
Multiple myeloma	Intravitreal anti-VEGF and steroid therapy for the management of retinal vascular disease associated with MM, a frequent occurrence.
Multiple system atrophy	Transcranial magnetic stimulation (TMS) has been found to improve motor symptoms in a number of parkinsonian disorders, but is less feasible as a basis

Disease Name	Therapeutic Device Suggestion
	for a lifelong ongoing treatment modality. Transcranial direct current stimulation (tDCS), however, a related, relatively novel, simpler, and less expensive/less heavily equipment dependent form of brain stimulation, could be more feasible for such lifelong and chronic therapy that these patients need.
Muscular dystrophies and spinal muscular atrophies	Modification of devices to help with ambulation for a longer period of time.
Narcolepsy	Attempting to assess the value of deep brain stimulation in enhancing alertness.
Neonatal diabetes	Likely no device needed. Better need for genomic identification and understanding of the disease. English workers at Essex Medical College have significant interest. Currently use sulfonamide instead of insulin.
Neonatal hemodialysis machine	There are two in production, one in Italy and one in England. These need to be brought to the USA for testing.
Neonatal kidney disease	Appropriate dialysis devices made specifically for neonates are needed.
Neonatal renal failure	Need safer and smaller methods for providing hemodialysis.
Nephrotic syndrome	We presently need targeted therapies to treat nephrotic syndrome.
Nephrotic syndrome and glomerulonephritis	There are very few targeted, precise therapies available for these conditions.
Neurodegeneration with brain iron accumulation	Deep brain stimulation—needs to [be] modified to allow flexible targeting and improved ability to recharge.
Neurofibramotosis	MR-HIFU with neurography and more precise targeting and ablation.
Neurofibromatoses	Generally, surgical intervention is sometimes needed for removal of tissue decompression resulting from the neurofibromas. Medical and surgical intervention may also be necessary for associated seizure activity.
Neurofibromatosis type 2	Neuroprostheses for hearing, vision, and movement.
Neurogenic orthostatic hypotension in primary autonomic failure	Compression garments are effective to treat neurogenic orthostatic hypotension but they suffer from very low compliance because they are impractical and cumbersome to use. In addition, the compression is permanently applied when patients wear them. A compression garment that applies compression only on standing (e.g., an inflatable compression garment activated on standing), and that is easy to put on would be a better device.
Neuroleptic malignant syndrome	ECT has been used but it is rather nonspecific and would be better to find a device that could target the symptoms.
Niemann-Pick type C	Port for intrathecal infusions of hydroxypropyl-beta-cyclodextrin.
Non-dystrophic myotonia	More therapeutic trials in NDM.
Normal pressure hydrocephalus	This is difficult until a better understanding of the pathophysiology is achieved.
Obstructed hemivagina with ipsilateral renal agenesis	Better surgical instrumentation to be able to respect vaginal septa, as well as better vaginal stints and molds to prevent restenosis are needed.
OCD	Closed-loop DBS, deep TMS.
Ocular chemical burns	Better ocular surface replacement and glaucoma treatment.

Disease Name	Therapeutic Device Suggestion
Organic acidemias	Disease modifying therapy is needed which is able to reach CNS. Solid organ transplantation has not been as effective as hoped. Gene replacement therapy may have a tolerable risk/benefit profile for MMA and PA.
Orthopedic problems associated with acromegaly	Create a device which can adapt to the constantly remodeling interface and respect the bending modulus of the implanted bone.
Osteogenesis imperfacta	Adaptable device that grows with child to protect against fracture yet avoids stress shielding and interference with epiphysis.
Osteogenesis imperfecta	Something that better treats the fractures by matching the OI characteristics, is modular and expandable, easily removed.
Osteogenesis imperfecta	We need better car seats and positioning devices to meet the needs of these patients
Osteogenesis imperfecta	Scoliosis stabilization device.
Osteogenesis Imperfecta	Ductile implants that could be used on those with very thin bones and bone deformities.
Osteosarcoma	Something noninvasive to allow limb salvage and improved survival.
Ovarian cancer	Need more effective adjuvant therapies.
Pancreas cancer	Biliary tree obstruction management, ablation in biliary tree.
Pancreatic cancer	Would like to see minimally invasive approach.
Pancreatic cancer	For premalignant or malignant disease, better therapeutic options for local therapy, such as EUS-guided therapy that is safe and effective.
Pancreatic cancer	Curative, non-invasive.
Pancreatic cancer	Don't know—but perhaps novel use of RF devices, light therapy, targeted therapy with addition of magnetic or RF applications.
Pancreatic cancer	Need a more specific means of targeting tumors and delivering localized therapy.
Pancreatic cancer	New chemotherapy needed.
Pancreatic cancer	Standard chemo regimens don’t work well. I am not an oncologist; will defer to them on this.
Pancreatic cancer	There are no highly effective treatments once pancreatic cancer has spread. This is a particularly virulent cancer.
Pancreatic cancer	This is beyond what I know about, but my patients with type 2 diabetes develop pancreatic cancer and it is missed.
Pancreatic cancer	We must discover unique molecular targets in pancreatic cancer and develop target-specific drugs, such as have been developed for breast and lung cancer.
Pancreatic cancer	We need a device to help treat patients with locally invasive and/or disseminated disease (stages III and IV). One idea is the use of electroporation or some sort of energy device that would selectively damage locally invasive cancers without injury to surrounding/adjacent tissues.
Pancreatic cancer	More effective and less invasive methods to treat PC would be [a] major advance.

Disease Name	Therapeutic Device Suggestion
Pathologic myopia	Engineer the device to work appropriately in a very elongated eye.
Pattern dystrophies of the retina	Chronic delivery of material that replaces abnormal genetic action leading to pattern dystrophy in the first place.
Pediatric acute kidney injury	Use standard clinical laboratory equipment to measure novel biomarkers.
Pediatric congenital hydrocephalus	Device to prevent ETV closure. Device to facilitate membrane fenestration during ETV. Device to enhance choroid plexus cauterization. New shunt technology that prevents obstruction.
Pediatric congenital heart disease	For pediatric populations: 1 yr–21 yr— there exists a huge need for 1. Heart valve repair devices. 2. Assist devices for failing Fontan patients. 3. New heart valve designs—only for the pediatric population. 4. Y-grafts for establishing physiologic blood flow back to the heart. 5. Oxygenators. 6. Cardiac ultrasonic transducers.
Pediatric esophageal atresia	Need a resorbable device that be used to deliver cells/growth factors for reconstruction of the esophagus.
Pediatric intractable epilepsy	No responsive neurostimulator currently available for children for epilepsy (is available for adults); deep brain stimulators not approved for pediatric epilepsy indications; newer implantable experimental epilepsy devices not approved for children.
Pediatric musculoskeletal and craniofacial anomalies	Ability to design and 3D print patient-specific devices for skeletal reconstruction is important in the pediatric space.
Pediatric OCT to measure retinal thickness in young children without the need for sedation	More efficient means of measuring retinal thickness without sedating the patient.
Pediatric solid tumors	MR-HIFU to improve local ablation and drug delivery.
Pediatric spinal dysraphism	Faster MRI, better physical comfort, easier use of video distraction.
Percutaneous therapies for single ventricle heart disease	Many different ideas...too many to list.
Pierre robin sequence	Device to lengthen mandible and/or relieve airway obstruction.
Polyarteritis nodosa	Paresthesias are common in PAN, but can often be met with undo skepticism amongst clinical providers. One means which in my view would be likely to identify a problem, would be simple placement of a hand or foot on an iPad or Android tablet. They often don't respond to touches, and I suspect that his is due to poor circulation. The ability to objectively demonstrate these types of problems for the extremities would be useful to the clinician... Assuming it works.
Pompes disease	New testing techniques to improve turnaround times.

Disease Name	Therapeutic Device Suggestion
Porphyria	Some protein or therapeutic that would "soak up" excess porphyrins so they would not exert a toxic effect on the nervous system. Currently hematin is only partially effective and it also requires an IV infusion.
Porphyria	Better treatment for prevention of AIP episodes.
Porphyrias (all types)	Current definitive treatment for acute porphyria is hemin—which can cause iron overload in those taking it recurrently over years; it also takes 2 days for relief from the crisis to occur. New research with siRNA are still undergoing clinical trials. I'd like to see a treatment device that has less side effects and has a faster treatment response.
Predicting and preventing SAH associated cerebral vasospasm and stroke	Biomarkers.
Pressure sores developing in persons with mobility disorders (e.g., paraplegia)	A new surface for people with movement disorders (cannot roll, cannot sense pressure or moisture) that will create a healing microenvironment to protect skin from breakdown and support healing in those who have had breakdown. This surface would have self-adjusting pressure, temperature, humidity, sheer and controls for avoiding development of ulcers/pressure sores. It would also alert medical professionals of unfavorable environment, sheer, humidity, or early development of sores so intervention could occur immediately.
Primary angiosarcoma of the breast	Correlate drug response to tumor genomics.
Primary ciliary dyskinesia	The vest is difficult to get approved for PCD due to lack of FDA approval for this disease.
Primary ciliary dyskinesia	Establish primary ciliary dyskinesia "indication" for use of the devices that promote airway clearance.
Primary ciliary dyskinesia	Airway clearance is central to treatment of disorders of mucociliary clearance, such as PCD or cystic fibrosis or non-CF bronchiectasis. We need more effective airway clearance devices. Similarly, we need more effective nebulizers and compressors for better peripheral deposition of inhaled drugs.
Primary ciliary dyskinesia	The disease results in a failure to adequately clear lung secretions. Several devices and therapies exist for clearing lung secretions and have been created to optimally work for cystic fibrosis. However, PCD is a different defect in clearance and it is not known if the current devices have equivalent efficacy or if there is a preferred device or possibly a modification that would work. For instance, the frequency of a therapy vest and time the patient utilizes it to clear secretions as well as overall efficacy is unlikely the same in someone with PCD and excellent cough clearance compared with someone with CF.
Primary hyperoxalosis	More rapid diagnosis from blood of abnormalities.
Primary immunodeficiency diseases	Therapeutic intervention by doing stem cell transplant from haploidentical donor requires T cell depletion. There is no FDA-approved stem cell selection/ T cell depletion device available.

Disease Name	Therapeutic Device Suggestion
Primary ovarian insufficiency	Need better info on appropriate dosages and safety, dosing required for managing hormone replacement for teens with—POI—also for puberty induction, as well as maintenance tx.
Progressive familial intrahepatic cholestasis	The need is for something to improve bile transport.
Progressive supranuclear palsy	Transcranial magnetic stimulation (TMS) has been found to improve motor symptoms in a number of parkinsonian disorders, but is less feasible as a basis for a lifelong ongoing treatment modality. Transcranial direct current stimulation (tDCS), however, a related, relatively novel, simpler, and less expensive/less heavily equipment dependent form of brain stimulation could be more feasible for such lifelong and chronic therapy that these patients need.
Progressive supranuclear palsy	Need treatment based upon better understanding of pathogenic mechanisms.
Progressive supranuclear palsy	Loss of postural reflexes and gait disorder with frequent falls are major issues in PSP. Devices that could promote continued safe ambulation and fall prevention would be a major contribution to patient care, including symptom management, quality of life, and preventing falls leading to major injury and death.
Pseudo-obstruction	A device that can locally increase neuronal activity or muscular activity to improve peristalsis. Can be a device that delivers medication locally to improve peristalsis
Pulmonary alveolar proteinosis	There is no currently approved pharmaceutical for pulmonary alveolar proteinosis; however, inhaled therapies are currently being proposed and evaluated outside of the U.S. Nebulizers for administration of this medication are available. However, the bioactivity of the medication before and after nebulization needs to be evaluated.
Pulmonary alveolar proteinosis	Need a better nebulizer device for the inhaled GMCSF drug.
Pulmonary alveolar proteinosis	Existing treatments are expensive, invasive, and suppressive. We need a treatment that is permanent.
Pulmonary alveolar proteinosis	Current therapy is a whole lung lavage of 15–30 liters of saline through a double lumen endotracheal tube in an operating theater. There must be an easier way to do this with specific lobar lavages, better access to inhaled GMCSF, or alternative therapies.
Pulmonary alveolar proteinosis (autoimmune)	Inhaled GMCSF.
Pulmonary atresia with VSD and multiple aortopulmonary collateral arteries	Combined surgical and non-surgical interventional approach to therapy that is tailored to specific patients.
Pulmonary hypertension	New device to percutaneously create a Pott's shunt.
Pulmonary hypertension	Requires invention of new technology either based on some sort of biophysical measurement or perhaps measurement of a blood biomarker level.
Pulmonary hypertension	Nitric oxide is used and is invasive.

Disease Name	Therapeutic Device Suggestion
Pulmonary insufficiency after tetralogy repair	Needs to reduce the size of the RV outflow and provide valve function.
Pulmonary Langerhans cell histiocytosis	Need effective targeted therapies
Pulmonary valve regurgitation	A catheter or surgically implantable valve grown from the patient's own pluripotential cells to create a new, long-lasting pulmonary valve replacement.
Pure autonomic failure	More usable and scalable device.
Pyruvate dehydrogenase deficiency	Pivotal trial to determine chronic safety and efficacy of dichloroacetate (DCA), an orphan drug previously used for this disease in open label studies.
Rapid onset dystonia-parkinsonism	These patients have also mutations in ATP1A3 just like AHC. Only a few of the mutations overlap with AHC. We believe that this is a pathway problem caused by the changing in this protein. The symptoms include dystonia, parksonism, dysphagia, gait problem, psychiatric, and seizures.
Rare brain tumors	Improved MRI technology should be able to distinguish normal tissue from abnormal tissue. Also, one should be able to determine whether a tumor is clinically active.
Rare diseases that are not diagnosed	Based on shorter, high-impact trials.
Rare kidney stone and mineral metabolism disorders	We need therapies that directly address the mechanisms underlying these disorders.
Rare pediatric airway	We need ways of maintaining an airway in a growing child. These would include airway stents, reconstruction devices, bipap. Conditions inside this category include congenital tracheal stenosis, subglottic stenosis (acquired and congenital), tracheomalacia, bronchomalacia, laryngeal webs.
Rare pediatric craniofacial syndromes	Creating modifications to devices to make them wearable by children with severe facial deformities: CPAP masks, glasses, hearing aids. These children often also have hearing loss, vision problems, and sleep apnea, for example.
Reflex sympathetic dystrophy (RSD)	It may be possible to repurpose current pacemakers and other neurostimulators to provide appropriate stimulus to the vagus nerve and sympathetic nerve change to improve the outcome for RSD patients. However, this is highly speculative and can only be approached by a case-by-case basis at this time, as patients' symptoms vary widely.
Relapsing polychondritis	No clinical trials are available and no real guidelines. Treatment is left on individual basis
Renal cancer	Ablation of hilar masses.
Respiratory failure in the newborn	Emphasis on an automatic oxygen adjustment module that will keep infants in a narrower oxygen saturation range and minimize complications associated with respiratory failure and prematurity.
Respiratory failure unresponsive to surfactant therapy	If we understand the disease due to a surfactant protein deficiency that is existent and not responsive to current surfactants, for example, it would help in

Disease Name	Therapeutic Device Suggestion
	elucidation of the disease, as well as have future implications for subsequent pregnancies.
Rett syndrome	Communication device for this non-verbal population.
Retinal degenerations, such as cone and/or rod dystrophies	This is complicated. Assuming that there was a proven drug that could halt the progression of degeneration, such a drug may be in need of a drug delivery device, so the drug could be delivered directly to the retina and/or supporting structures.
Retinitis pigmentosa	Gene therapy and stem cell transplants may be options.
Rett and Rett-related disorders	Adaptive communication devices need to be standardized and provided more widely. Current MCD rules preventing switch from one device to another are cumbersome.
Rett syndrome	We need something that will actually modify or cure this disease. We know this can be done in the animal models.
Rett syndrome	System to improve non-verbal communication.
Rett syndrome	Device for parasympathetic stimulation or comparable instrument restoring autonomic balance.
Rett syndrome	Communication dysfunction requires advanced technologies (computer-based). Although devices exist, these greatly need sophisticated improvement and development of new models to ease use of patients, caregivers, teachers, and therapists.
Right ventricular outflow tract dysfunction (pulmonary regurgitation)	We need larger devices to treat nonconduit RVOTs. Currently, existing percutaneous pulmonary valves are too small for many RVOTs. Device will need to be retrievable, probably self-expanding and of reasonable size to be placed in blood vessels.
ROHHAD syndrome	Enable use of hiflo and other non-invasive airway support for home.
Sarcoma	Devices to kill tumor that is not easily resected due to proximity of vital structures. More precision in ridding patient of tumor without damage to vital structures.
Severe epilepsy of infancy	Reliable, tolerable, and effective means of neuromodulation.
Severe heart failure in children	Fully implantable ventricular assist device with the ability to work in univentricular hearts.
Short QT syndrome	Left stellate ganglion stimulator to prolong QT interval.
Sickle cell	Separate out the sickle cells and provoke normal hemoglobin.
Sickle cell	Determine the severity of sickling occurring and the response to treatment.
Sickle cell disease	A useful device would identify the sickle cell patient as a significant responder to epoetin alfa (Procrit) in the treatment of complications of the anemia (e.g., cutaneous ulcerations). This therapy is currently restricted for other uses in the U.S. but should be expanded. It would appear, however, that a diagnostic for selective therapy application is needed first.

Disease Name	Therapeutic Device Suggestion
Sickle cell disease	We struggle to effectively treat pain crisis in this population, in part as pain assessment is subjective, and in part as the interventions (parenteral pain medication) have limitations.
Sickle cell disease	More therapies are needed, as only bone marrow transplant and hydroxyurea are the only approved therapies for sickle cell disease.
Sickle cell retinopathy	Laser can be done to treat advanced retinal changes. We need an earlier intervention to prevent that advanced proliferative stage.
Sickle cell disease	Greater use of stem cell transplantation. More effective preventative and therapeutic maneuvers for sickle crises.
Significant left main CAD	Current stents do not come in the length to treat left main CAD, as the left main artery is if variable length and it is not desirable to have stent in the aorta.
Sitosterolemia	Plant sterol detector for food to control plant sterol dietary intake.
Sjogren syndrome	No effective treatment for Sjogren exists.
Sjogren syndrome	Using ELISAA or PCR of a battery of markers to confirm the diagnosis.
Skeletal dysplasia	Need smaller devices.
Skeletal dysplasias	Device for scoliosis therapy.
SLOS	Sensor-based biomarker analysis system to monitor therapeutics efficacy.
Smith-Lemli-Opitz syndrome	What's needed is a method for direct delivery of cholesterol to the brain of those with SLOS. This could be an implantable pump. What would also be needed is a safe source of cholesterol to load into the pump.
Soft tissue sarcomas	Improve soft tissue grafts (muscle flaps, skin grafts, nerve grafts, etc.) to facilitate reconstruction.
Sphincter of Oddi dysfunction	Meta-analyses/Cochrane reviews, etc. to formulate probability. Table to limit invasive testing; better data on who responds to sphincter ablation.
Spinal AMV	More flexible and steerable catheter system to get into small distal tortuous vessels.
Spinal muscular atrophy	Try to create a more portable ventilator for families who choose tracheostomy and ventilator for their children.
Spinal muscular atrophy	Devices to improve limb functionality—exoskeleton?
Spinal muscular atrophy	Device move limbs through EEG control.
SSADHD	Seizure-sensing device that would release anti-seizure drugs during seizures.
Stevens-Johnson syndrome	Better corneal replacement technique/device.
Sturge-Weber syndrome	Device that delivers drug (or gene therapy) targeting pathways hyperactivated by somatic mosaic mutation in GNAQ to effected regions in the brain.
Sudden cardiac arrest	Existing implanted defibrillators have some serious and relatively common complications; improved devices would reduce these risks (e.g., infection) and make them more attractive for younger patients.
Syndromic craniosynostosis	After blood testing for FGFR-related abnormality, insertion of a gene repairing the deficient FGFR, allowing normal cranial growth/treatment of the condition without surgery.

Disease Name	Therapeutic Device Suggestion
Takayasu's arteritis	Similar to my responses regarding diagnosis, better imaging techniques can improve the follow-up for these patients. This is desperately needed as there are poor biomarkers available.
Tardive dyskinesia	In its worst form, it can be very disabling and since it is part of the dopamine system, there could perhaps be devices that could provide stimulation to decrease the increased tone.
Temporal lobe epilepsy	Implantable local drug-delivery device.
Thallasemias	Gene therapy.
The porphyrias	Make heme arginate readily available for use in the USA, as it is in Europe, Australia, etc. Reconstitute Panhematin in human serum albumin, as described by Bonkovsky et al. [*Amer J Gastro*, 1991] and updated by Anderson, Bonkovsky et al. [*Ann Int Med,* 2006].
Third-degree burns	Get ReCell and StrataGraft through the FDA process ASAP and on the U.S. market.
Tourette's syndrome	Start with closed loop DBS for intractable cases.
Toxic epidermal necrolysis (TEN) or Stevens-Johnson syndrome	Although IVIG was proposed to heal the skin lesions of TEN several years ago, observational studies have not supported its efficacy. What we need is a skin treatment device that will (a) bring about faster skin healing, and (b) most importantly, bring about resolution of the multiorgan failure that is the principle cause of death.
Tracheobronchomalacia pediatric and adult	3D printed resorbable splints and stents.
Transcatheter ASD device (cardiac)	Use of new biomaterials to improve biocompatibility; take advantage of bioresorptive technology; utilize 3D printing technology.
Transverse vaginal septum	Adolescents who have surgery for vaginal transverse septa are at risk for vaginal stenosis. Current stints are cumbersome and difficult for these girls to use. An appropriately sized and configured vaginal stint is needed to prevent restenosis after surgery to remove transverse vaginal septa. Bioengineering needed to develop the materials and the correct configuration—the vagina is (not) a cylinder, and thus current dilators and stints do not fit the vagina well.
Trigeminal neuralgia	Minimally invasive implant for decompression of the trigeminal nerve.
Triple negative breast cancer	Primarily, new drugs are needed, more innovative strategies to treat local regional disease that would better prevent local recurrence.
TTP	Ideally, an ADAMTS13 concentrate would speed recovery and decrease mortality.
Type A carotid cavernous fistula	As before, detachable balloons are an excellent and economical method of treating this disease but none are available in the U.S.A. As in the case of aneurysms that would otherwise warrant sacrifice of the ICA, an endovascularly deployable covered stent that could be readily positioned in the cavernous ICA and fully expand to assure wall adhesion would be a novel method of treatment, but it does not exist.
Unknown diagnosis so need whole exome sequencing	The more we know about underlying genetic etiology, the more likely we are to find therapies.

Disease Name	Therapeutic Device Suggestion
Urea cycle defects	Home measurement of metabolism.
Urea cycle disorders	Device to deliver chimeric enzyme protein to liver hepatocytes.
Urea cycle disorders	Continuous ammonia monitor or single time point portable ammonia monitor.
Vascular obstructions in children	Stents with increased potential for redilation and/or resorbable to account for somatic growth.
Viral infections of the CNS particularly in immune suppressed patients	Need new methods for delivery of drugs across the blood brain barrier.

APPENDIX G: LIMITATIONS TO CURRENT DIAGNOSTIC DEVICES

Disease Name	Limitations to Current Diagnostic Devices
Acoustic neuroma	Selection of when to do an MRI is not clearly determined. The cost and wait time is cumbersome for the patients and distressful.
Active tuberculosis developing from latent infection	GeneXpert is used for active TB and QFT is used for latent TB, though the latter is an indirect immunologic test.
Acute cardiopulmonary failure in children (necessitating mechanical support like ECMO/VAD/etc.)	BNP is the most common biomarker used for heart failure in children. There is some evidence for its use in pediatrics, but it is mostly based on finding missed congenital heart disease patients. It requires a blood sample, which many adult centers are not able to acquire from small children.
Acute intermittent porphyria (and other acute porphyrias)	For rapid diagnosis in patients presenting with acute symptoms.
Acute renal failure in children	We are limited to using creatinine as a biomarker for acute renal failure. As has been described thoroughly in the medical literature, it is not a good biomarker candidate, for among other reasons having a late peak after injury. We need improved sensitivity and specificity biomarkers that peak early after injury.
Alpha 1 antitrypsin	Lack of availability, cost, lack of third-party payors' coverage.
Alpha 1 antitrypsin deficiency	There is a need to improve therapeutic outcome for these patients.
Alpha one antitrypsin	The test does not predict prognosis.
Alport syndrome and other genetic nephritides	Most definitive test is invasive (biopsy) or very expensive (genetic testing).
Amyotrophic lateral sclerosis (ALS)	Not sensitive in early stages.
Amyotrophic lateral sclerosis	EMG only evaluates lower motor neuron degeneration, not upper motor neuron.
Amyotrophic lateral sclerosis	Electromyography lacks specificity and sensitivity. Imaging and blood tests performed in conjunction with electromyography are performed to rule out other diagnoses, rather than to confirm the diagnosis of ALS.
Amyotrophic lateral sclerosis	ALS remains a clinical diagnosis, but EMG can be useful in demonstrating the presence and distribution of lower motor neuron pathology in those with little to no clinical evidence of lower motor neuron signs. The major limitation is patient discomfort.
Anterior chest wall deficiency syndromes	Subjective.
Aortitis	Altered wall biology or luminal changes seen on imaging are not specific for aortitis. Need to differentiate from atherosclerosis and other non-inflammatory conditions.
Atypical hemolytic uremic syndrome (aHUS)	With standardization, we would know the sensitivity and specificity of such testing. And again, many of my patients will not be able to pay for rare disease testing (nor will their Medicaid insurance authorize such testing).

Disease Name	Limitations to Current Diagnostic Devices
Atypical HUS	Principally, we start with ADAMTS13; if it is normal, we then must investigate other causes of a thrombotic microangiopathy, such as abnormalities in complement components or genes.
Autoimmune pulmonary alveolar proteinosis	We have developed and validated a sandwich ELISA for the diagnosis of autoimmune PAP that is 100% sensitive and 100% specific for this disease (among all people, including various other diseases associated with PAP syndrome). The test is currently performed as a clinical research test under a clinical research written informed consent.
Autoimmune pulmonary alveolar proteinosis	CT, bronchoscope (bronchoalveolar lavage, biopsy), other serum markers.
Autosomal recessive polycystic kidney disease (ARPKD)	Renal ultrasound needs to be repeated and can vary in its interpretation. Genetic testing is not always available for outpatients due to insurance barriers.
Avascular necrosis	Radiation. Requires testing multiple body parts.
Basal cell nevus syndrome	We piece together a diagnosis from clinical, radiologic, and occasional genetic information. It is a best guess.
Birt–Hogg–Dubé disease	Expensive and not completely diagnostic.
Bone cancers (osteosarcoma, lymphoma)	Invasive and costly and time-limited.
Bone marrow failure syndromes	Slow, generally have to test for one at a time. Sending panel would be quicker and perhaps cheaper.
Bone sarcomas	Imaging studies often nonspecific, with different neoplastic and non-neoplastic entities sharing common features on x-ray, CT, and MRI. Histology from biopsy samples may be difficult to interpret; undersampling during biopsy may result in understaging of disease.
Cadasil	Not easily available or comprehensive.
Cardiac sarcoid	PET, CT, CMR all suboptimal for diagnosis and biopsy invasive and also has poor sensitivity.
Cardiac sarcoid	MRI and PET not specific for sarcoid.
Charcot-Marie-Tooth disease	Very expensive and misses some patients.
Charcot-Marie-Tooth disease	Nerve conduction velocity testing can determine whether the disease is demyelinating or axonal but doesn't give the exact cause. Genetic testing does often give the cause, but it is expensive and many disease causing genes and variants are unknown.
Charcot-Marie-Tooth disease	Very expensive. Current available genetic testing misses around one-third of cases.
Childhood nephrotic syndrome	The approved device is a biopsy needle, therefore the test is invasive.
Chronic exertional compartment syndrome	Invasive, moderate accuracy.
Chronic graft-versus-host disease	They're nonspecific and insensitive.
Chronic granulomatous disease	Tissue biopsy needles.

Disease Name	Limitations to Current Diagnostic Devices
Combined immunodeficiencies	Currently available techniques to diagnose these diseases are very poor. A lot of research in techniques and genetic analysis are necessary in order to improve our treatment for this population.
Congenital diaphragmatic hernia	Need to use magnetic resonance imaging to avoid fetal radiation exposure; need to develop non-invasive strategies for isolation fetal DNA.
Congenital disorders of glycosylation	In some cases there may be a limitation in diagnosing cases of CDG type 1a.
Congenital heart disease	For early accurate intrauterine diagnosis of congenital heart disease and treatment, there are two things that must converge: 1) accurate high-resolution imaging and 2) devices and procedures to correct defects during fetal cardiac development.
Congenital hydrocephalus	Direct tools to measure ICP are invasive and require surgery.
Congenital limb deficiencies, tibial and fibular hemimelia	Real need is for etiology research.
Cornelia de Lange	DNA sequencing tests do not identify all clinically diagnosed patients. Either we don't know all the genes or current tests do not adequately evaluate known genes. Cornelia de Lange is just an example, as there are many other similar conditions with same limitation.
Cowden syndrome	Finding a PTEN mutation means high risks of organ-specific cancers (see my previous comments), but at an individual level, we still cannot predict which particular cancers any single PTEN mutation carrier will or will not get in a lifetime.
Cystic fibrosis	These are maternal serum screening for carrier status of the CF gene mutations – so they only involve maternal status. If positive carrier, then get to test father and finally the fetus. So a long timeline and the final fetal testing is currently invasive.
Cystic fibrosis	Unreliable.
Cystic fibrosis (many different mutations)	Current diagnosis is sweat chloride screening.
Cystinosis	Measurement of white blood cell cystine levels are only performed in 2 labs in the US. Very cumbersome and expensive.
Dent disease	Cannot identify mutations in 20% of cases.
Desmoid	They are lacking in accuracy and greatly underestimate the extent of disease.
Desmoid tumors	MRI and US.
Dyskeratosis congenita	DNA sequencing and telomere length analysis.
Dystonia	The blood tests help with certain forms of dystonia. Most forms of dystonia do not have a genetic test. If the DaTSCAN were able to be "retooled" to help diagnose dystonia, it would be helpful.
Dystonia	Insurance coverage.
Early onset scoliosis	X-rays and physical exam.

Disease Name	Limitations to Current Diagnostic Devices
Ebstein's anomaly	Cardiac ultrasound is limited in its ability to predict which patients may do better with a single- versus two-ventricle surgical approach, and we don't really know how to improve sensitivity and specificity because of lesion rarity in any single institution.
Ehlers-Danlos disease	Identification of additional individuals may increase the number of individuals exposed to radiation for screening examinations, but the treatment is mostly physical therapy and meticulous surgical hemostasis, thereby preventing complications of the disorder.
Eosinophilic colitis	It's a patchy disease and biopsy interpretation must be improved.
Eosinophilic esophagitis	Using upper endoscopy with biopsies to diagnose eosinophilic esophagitis is invasive, requires sedation, has societal costs given need for patient and patient's ride to miss work. Furthermore, test is nonspecific in that it only finds features of eosinophilic esophagitis which can be seen in other conditions.
Eosinophilic esophagitis	Upper endoscopy is invasive and, in pediatrics, is most often performed under general anesthesia. Scheduling a patient for upper endoscopy leads to missed school and work days. For those trying elimination diets, the cycle of trial and error food elimination followed by diagnostic EGD is cumbersome and burdensome.
Eosinophilic esophagitis	The disease is patchy and may be missed if insufficient numbers of biopsies are obtained.
Eosinophilic esophagitis	Requires invasive test (endoscopy) with biopsy.
Eosinophilic esophagitis	Molecular PCR based diagnostics.
Eosinophilic esophagitis	Endoscopy.
Eosinophilic esophagitis	EndoFlip = distensibility measurement device.
Eosinophilic esophagitis	Costly; invasive; potential risks; time consuming.
Eosinophilic esophagitis and eosinophilic gastrointestinal disorders (in general)	Requires endoscopy and varied forms of anesthesia.
Eosinophilic gastritis	The disease is patchy and may be missed if inadequate/insufficient numbers of biopsies are obtained.
Eosinophilic gastroenteritis	Invasive.
Eosinophilic gastroenteritis	Cost; time; potential complications.
Eosinophilic gastrointestinal disease	The device/procedure needs to be done under anesthesia.
Eosinophilic gastrointestinal disorders (EGID)	Invasive procedure that requires sedation and can be associated with side effects such as bleeding, or rupture of the esophagus. The procedure is also costly for families.
Eosinophilic GI disease	All existing clinical tests require endoscopy and biopsy with need for sedation/anesthesia/expense/risk.
Esophageal adenocarcinoma	Upper endoscopy - expense and inconvenience.
Ewing sarcoma	Imaging being my tool is not always specific.
Extreme microcephaly	Need to use magnetic resonance imaging to avoid fetal radiation exposure.

Disease Name	Limitations to Current Diagnostic Devices
Fabry disease	Genetic testing does not provide for the needs expressed above. Tests like serum creatinine, urinary protein, Holter monitor become abnormal when there may already be severe damage. Estimates of risk (e.g. for females) are inadequate.
Fabry's	Renal biopsy is invasive.
Familial exudative vitreoretinopathy	Current optical coherence tomography devices and most cameras need to be within about 2 cm of a child's eye. This is impossible in a very young toddler without sedation/anesthesia. Angiography also requires sedation/anesthesia. To diagnose and monitor disease, this requires repeated examinations under anesthesia and risks missing progression of disease during intervals between examinations.
Familial LCAT deficiency	Not validated.
Esophageal cancer	Far more accurate clinical staging of esophageal cancer—a rare disease—that affect treatment decisions. Esophageal ultrasound and even fine needle aspiration do not accurately characterize early stage (stage T2 and less) cancers, which is critical in improving survival of these patients.
Fatty acid oxidation disorders	Most are too slow or cumbersome.
Focal dystonia	Need better sensitivity and specificity. Not widely available.
Focal segmental glomerulonephritis	Kidney biopsy is invasive. Occasionally, insufficient tissue is obtained. Fibrosis does not allow for diagnosing the etiology for FSGS.
Focal segmental glomerulosclerosis	Renal biopsy alone cannot differentiate primary FSGS from secondary.
Focal segmental glomerulosclerosis	It cannot be scaled up.
Focal segmental glomerulosclerosis	Invasive, can miss early FSGS and appear as MCD, may not distinguish subtypes of FSGS.
Focal segmental glomerulosclerosis (FSGS)	Proteinuria as a nonspecific test of renal damage.
Focal segmental glomerulosclerosis (FSGS)	Histological lesion may result from many different diseases leading to the same pathology. More granularity would allow for better patient stratification and subclassification.
Gaucher's disease	Often the diagnosis is not made until bone marrow biopsy, which is mildly invasive and inconvenient for patient and health care practitioner and requires training and knowledge and expertise for safe execution, etc.
Primary immunodeficiency disorders	Gene testing and WES sequences exons, would be helpful to include introns as well (WGS). Panels for disease states are helpful rather than select single gene Sanger sequencing. However, the panel may not include all the genes that may be helpful.
Genetic disorders of surfactant metabolism in newborn infants	For extracorporeal lung device, limitations include need for anti-coagulation; for genome editing, limitations include possible off target effects; for prenatal genomic testing, no limitations.
Giant cell arteritis	Temporal artery biopsies are invasive and not very sensitive.
Glutaric aciduria	Unless it is a florid case, these may miss the diagnosis.

Disease Name	Limitations to Current Diagnostic Devices
Graft-versus-host disease	Endoscopic GI biopsies, liver biopsy, skin biopsy. All have inherent risks and the pathology findings are not always specific, in particular in the presence of an active infection.
Granular corneal dystrophy	Too slow and expensive and inconvenient.
Heart failure in small children	Spotty availability of echo equipment and expertise. As an alternative, wider distribution and expertise with handheld echo could also be a very reasonable approach.
Heart failure with preserved ejection fraction	Successful new test may result in increasing numbers of patients, which have limited access to a scarce resource (donor hearts).
Hereditary Hemorrhagic Telangiectasia (HHT)	The limitations include early diagnosis by imaging to identify patients who may be treated with drugs to prevent progression of disease. For example, we can now identify if a patient has the gene for one of the HHTs. We can sometimes identify changes in imaging based on CT of the lung. However, we do not have a drug which prevents the progression of HHT to where the patient requires a surgical procedure to treat epistaxis, or embolization to prevent a stroke or heart failure.
Hereditary retinopathy	Cumbersome and nonspecific.
Heritable pulmonary arterial hypertension	Incomplete array of mutations.
Heterotopic ossification of wounds	The results provided by current technology are qualitative and not quantitative.
Huntington disease	See prior box. The genetic test does not inform patients about age of onset of symptom, severity of symptoms, range of individual symptoms. For some (intermediate alleles), the mutation is partially penetrant, so the test does not confirm whether or not a presymptomatic person will develop HD in the future, although it can confirm HD as the cause of a classic clinical picture in a symptomatic person.
Huntington's chorea	Unreliable.
Huntington’s disease	Genetic testing.
Huntington's disease	Genetic test for confirmation purposes.
Hypersensitivity pneumonitis	Poorly specific and not very sensitive.
Hypertrophic obstructive cardiomyopathy	Septal ablation using alcohol and standard POBA balloons. Could be greatly improved to enhance the safety of this approach.
Idiopathic intracranial hypertension	MRI can't measure pressure, lumbar puncture is dependent on multiple factors that can alter CSF pressure during measurement and is technically difficult in the morbidly obese who represent a large portion of these patients.
Idiopathic nephrotic syndrome	Do not distinguish clinical behavior (responsiveness to treatment) or specific subtype of NS. Do not indicate forms associated with loss of kidney function.

Disease Name	Limitations to Current Diagnostic Devices
Idiopathic pulmonary fibrosis	X-ray will show characteristics of fibrosis and biopsy may confirm type or category, but if the etiology is unknown hence idiopathic, the type of unknown fibrosis can be large and untreatable therefore more research to identifying the causes and types will help find the instruments and tools to provide the right diagnosis for the type of fibrosis and chip away at the idiopathic group. Ability for precise disease identification and cause, will help get closer to a needed cure.
Idiopathic pulmonary fibrosis	Patients are often too sick to get a lung biopsy.
Idiopathic pulmonary fibrosis	Confident diagnosis in only 50% of cases.
Idiopathic pulmonary fibrosis (IPF)	HRCT of the chest is sued to diagnose and this suffices in about 50–70% of cases, but is not specific many times. In some (20–30%) cases, a surgical lung biopsy is required.
IgA nephritis	Proteinuria as a nonspecific test to renal disease severity.
Inborn errors of metabolism	Many are not FDA approved and are not considered clinically validated, since validation can be onerous.
Inherited retinal dystrophies	There is no standard test panel and the range of genetic abnormalities can be broad.
Interstitial lung disease	Main limitation of lung biopsy is the invasive nature; need something less invasive.
interstitial lung diseases	Current standard of diagnosis depends on surgical lung biopsy with attendant risks.
Intraocular lymphoma	Vitreous biopsy pathologic testing is used and frequently the results are nondiagnostic or inconclusive.
Jarcho-Levin	VEPTR: Longitudinally expands chest, but not in transverse plane, and marked growth in length of the thoracic spine is needed, but not possible with current device.
Jeune	Not specific in determining prognosis as listed.
Kawasaki disease	Very nonspecific marker of inflammation and clinical markers, which are also very nonspecific as individual observations. The diagnosis requires a constellation of clinical tests and physical observations, which have been demonstrated to be associated with coronary artery dilation.
Larsen's syndrome	Availability of testing.
Laryngeal dystonia	Inadequate.
LCAT deficiency	There is no direct assay for LpX.
Leukoencephalopathies	Imaging devices (MR) are not fine-tuned for this patient population.
Leukodystrophies with the exception of adrenoleukodystrophies	Most people are not aware of them and do not know how to diagnose these conditions.
Long QT syndrome	Incomplete for all forms of LQTS.
Low grade chondrosarcoma	Ultimate diagnosis is currently made pathologically with correlation with radiologic imaging. The pathology and radiology are sometimes not quite certain.

Disease Name	Limitations to Current Diagnostic Devices
Lymphangioleiomyomatosis (LAM)	Serum test is expensive. Sometimes it may be missing diagnosis.
Lymphangioleiomyomatosis	Many, but not all, women have an elevated VEGF-D; we also rely heavily on CT to diagnose the disease, but it's not entirely specific and so we often have to proceed to biopsy anyway.
Lymphangioleiomyomatosis	VEGF-D levels in blood are measured. They are not sensitive very high levels are specific for the disease.
Lymphangioleiomyomatosis	The single laboratory closed for more than 1 month this past year. Sensitivity of the VEGF-D test is only 50%. We need something better.
Lymphangioleiomyomatosis	The only test that is diagnostic is a lung biopsy or analysis of pleural fluid.
Lymphangioleiomyomatosis	The diagnostic tests currently available include a genetic test (using peripheral blood), a biological marker assay from peripheral blood, and tissue (lung, kidney, skin, lymph node) biopsy with pathology analysis. The biopsy testing is invasive. The blood based testing has limitations in sensitivity.
Lymphangioleiomyomatosis	Test is an ELISA. Sample requires processing—serum separation prior to shipment to the site where assay is done. Results not readily available.
Lymphangioleiomyomatosis	Serum must be sent to offsite lab that has limited kits and long turnaround times. In addition, there is a significant false negative rate.
Lymphangioleiomyomatosis	Poor sensitivity of VEGF-D blood test; poor sensitivity of transbronchial biopsy; invasiveness of surgical lung biopsy.
Lymphangioleiomyomatosis	Pathological diagnosis is invasive. Serum measurement is invasive.
Lymphangioleiomyomatosis	Not FDA-approved.
Lymphangioleiomyomatosis	Limited sensitivity and specificity.
Lymphangioleiomyomatosis	Lack of sensitivity and specificity.
Lymphangioleiomyomatosis	Histopathology is the gold standard but very invasive. We cannot access VEGF-D at our institution, as we have no money. CT is good but not sufficiently specific and not so good in patients who have smoked. The ERS guidelines for diagnosis are helpful but need to be updated.
Lymphangiomatosis	One of the diagnostic tests, open lung biopsy, may be more invasive; many patients can't accept this test.
Lymphangiomatosis	Biopsy-based diagnostic testing is invasive and cumbersome.
Lymphangiomyomatosis	Not specific.
Lysosomal storage diseases	Currently no good multiplex test.
Mal de débarquement syndrome	An ENG is very nonspecific and does not get at an underlying understanding of the pathophysiology.
Many tropical infections (e.g., loa loa)	See previous response - current serologic tests do no distinguish between filarial diseases.
Mastocytosis/mast cell activation syndrome	It captures most mastocytosis, but misses some and misses most MCAS.
Maturity-onset diabetes of the young (MODY)	Cost.

Disease Name	Limitations to Current Diagnostic Devices
Melanoma	Don't assess with great specificity prognosis. Sentinel node bx good test for node involvement but requires surgery.
Mesenteric venous thrombosis	Not aware of laparoscopically applicable venous monitoring device.
Minimal change disease	Requires a kidney biopsy.
Minimal change disease	Nonspecific parameter of renal damage.
Mitochondrial disease	Improved, but complex and cumbersome. No way to quantify/monitor degree of disease or response to therapy.
Mitochondrial diseases	Limited sensitivity and specificity.
Mitochondrial diseases	Cost and specificity.
Mitochondrial disorders	Simple available screening blood tests are not specific so many patients undergo invasive muscle biopsy. DNA screening is expensive, often not covered by insurance, and take weeks-months to get results.
Mitochondrial disorders	Not sensitive or specific enough yet.
Mitochondrial disorders	Next generation sequencing panels and whole exome sequencing. We need better biomarkers to validate variants of unknown significance.
Mitochondrial respiratory chain deficiency	Current devices are not reliable.
Moderate and severe pediatric traumatic brain injury	Children can't stay still or are frightened by machine, so often get CT scans which don't give as much useful diagnostic information and also include radiation. MRI likely should be the test of choice, but is not adapted/modified for the needs of children. Video can distract children and help them remain still but is cost-prohibitive because of MRI compatibility requirements. Prioritizing faster, targeted sequences, and MRI-compatible distraction techniques or other adaptations for children could make this a much better diagnostic tool with fewer adverse side effects which are worse for children (e.g., radiation with more toxicity in younger patients).
Mucopolysaccharidoses (newborn screen)	Conditions cannot be diagnosed until clinically evident. There is currently no newborn screen.
Mucus membrane pemphigoid	Less sensitive and specific than desired.
Muir Torre	None, just slow and not always accurate.
Multiple myeloma	Slow.
Multiple congenital anomaly syndrome	Genome wide array turn-around time is 2-4 months and not reimbursed by insurance for hospitalized patients.
Multiple myeloma	Too expensive, time-consuming, and cumbersome.
Multiple myeloma	Pain.
Muscular dystrophy	Cost.
Myasthenia gravis	Sensitivity of serological assays (especially in those with ocular myasthenia) is quite limited. And both the sensitivity and specificity of electrodiagnostic tests for MG (especially ocular MG) are quite limited.

Disease Name	Limitations to Current Diagnostic Devices
Myocarditis in children	Risk of anesthesia for the procedure. Perforation of the heart during biopsy, especially in the infant. Arrhythmias/VF during the catheterization. Damage to the tricuspid valve during biopsy. Inconclusive results do not rule out myocarditis.
Myopathies	MRI is very sensitive but not specific.
Neonatal renal failure	Serum creatinine is too late a finding.
Nephrotic syndrome	Not specific enough to inform what variants of disease are present and in what phase.
Nephrotic syndrome and glomerulonephritis	Kidney biopsy (the gold standard) is invasive, especially for children who require anesthesia for this procedure. There is not universally available genetic testing.
Neuronal ceroid lipofuscinosis	Lack of availability of sufficient expertise and lack of affordable access.
Non-dystrophic myotonia	Not helpful in confirming NDM type.
Non-invasive devices for neurocritical care monitoring of cerebral perfusion	With consent only. Research protocols for several disorders, but many more populations could potentially benefit.
Non-ketotic hyperglycinemia	Timeliness of results.
Normal pressure hydrocephalus	High volume lumbar puncture is specific: when it leads to improvement, the patient will do well. However, it has poor specificity - there are too many false negatives.
Obstructed hemivagina with ipsilateral renal agenesis	Current screening of pts with pelvic pain may suggest hematocolpos, but often only after significant time and pain does further imaging with MRI suggest the diagnosis.
Osteosarcoma	Invasive, sometimes inconclusive.
Ovarian cancer	Sonar and CA125 nonspecific.
Ovarian cancer	CA125 level.
Pancreatic cancer	Unreasonable to routinely use early. Becomes a confirmatory test, but is usually too late for a cure.
Pancreas cancer	Poor sensitivity and lack of specificity.
Pancreas cancer	Needle biopsy.
Pancreas cancer	CEA has an accuracy of about 80% to predict potential for malignancy only, for pancreatic cystic lesions. In addition, there is no test for early detection of pancreas cancer, potentially early enough that it can be resected prior to development of micrometastases.
Pancreatic cancer	Usually these devices are applied when the patient is symptomatic. By then, it is usually too late for effective treatment.
Pancreatic cancer	Unreliable.
Pancreatic cancer	Unavailable for screening.
Pancreatic cancer	The main limitation is insensitivity. The tumors are not readily seen until they are ~2 cm in diameter, at which point most have already metastasized.

Disease Name	Limitations to Current Diagnostic Devices
Pancreatic cancer	Radiologic modalities are helpful but are used once a patient develops symptoms. They are not necessarily specific. Endoscopic methods are invasive and carry risks.
Pancreatic cancer	PCa currently is detected too late. 5-year survivals remain dismal.
Pancreatic cancer	Only late-stage, terminal disease diagnosed.
Pancreatic cancer	MRI can pick up some lesions, but most are on the order of 1 or more cm--think we need to find tumors earlier.
Pancreatic cancer	It's usually too late to treat pancreatic cancer once this device is used for diagnosis. Need a test that diagnoses pancreatic cancer sooner so that it can be treated sooner.
Pancreatic cancer	If not specific, will lead to high number of invasive bx procedures.
Pancreatic cancer	Currently use CT scan for diagnosis. This has limited sensitivity and specificity.
Pancreatic cancer	CT, MRI, and PET-CT all limited by resolution and specificity.
Pancreatic cancer	CT and MRI have high cost and CT uses radiation. Patients usually have no symptoms until advanced stage. A cheap low-cost test sufficiently sensitive to catch early stage disease is needed.
Pancreatic cancer	CT/MRCP/ERCP/EUS/CA 19-9....
Pattern dystrophies of the retina	They do not automatically identify pattern dystrophies, so that expertise around the country or world is needed for correct diagnosis.
Pediatric congenital hydrocephalus	MRI requires sedation/anesthesia in young children. Measurement of ICP requires an invasive procedure.
Pediatric congenital heart disease	Fetal echocardiography is not sensitive or specific enough to capture all cases of congenital heart disease. Thus, many children are missed. It is also operator dependent, and operator skill plays a large role in its effectiveness as a screening tool.
Pediatric intractable epilepsy	Heavy, painful, prone to infection because of need to tunnel wires from intracranial to extracranial space, too big for young children, prone to CSF leaks, prone to wound complications, prone to movement because of tugging on external wires, require bedrest and intensive care stay for duration of monitoring (usually 1 week or more).
Pediatric solid tumors	Patient and device size mismatch.
Pediatric spinal dysraphism	Studies are too slow with current techniques and therefore require general anesthesia in many instances. This would be improved for older children if distraction techniques were available (e.g., video) or sequences were shorter, OR if MRI scanner were less frightening for children.
Pediatric upper airway obstruction	Not specifically geared for children, and need specific modification. Too invasive for non-ICU setting.
Porphyrias	Test needs to be done during a crisis, when patients are too sick to leave their homes. Many ERs and hospitals are not familiar with the tests.

Disease Name	Limitations to Current Diagnostic Devices
Porphyrias (all types)	It takes up to 7 business days to get results of urine porphobilinogen and aminolevulinic acid in a standard laboratory. Our genetics lab has been able to perform it in 2 business days, but that is still a lot of time spent waiting to make a diagnosis in someone with acute porphyria. Plasma and urine porphyrins take up to a week for results to become available in a standard lab.
Prader Willi	Turn-around time is 2–4 weeks.
Primary (inherited) immunodeficiencies	Have to test for one or two genetic causes at a time. Take too long in light of clinical urgency.
Primary ciliary dyskinesia	Can only be used under research protocol, very expensive.
Primary ciliary dyskinesia	The two current gold standards for diagnosing PCD are cilia biopsy and genetic testing. Neither are perfect, though. Cilia biopsies can only diagnose ~70% of individuals with PCD. We believe that approximately 30% of individuals with PCD have 'normal' cilia biopsies. And genetic testing is still not absolute either. Complete genetic testing of 35 known PCD genes still probably only accounts for ~70% of individuals with PCD. We are still learning and discovering additional PCD genes and mutations.
Primary ciliary dyskinesia	The main limitation is the lack of FDA approval.
Primary ciliary dyskinesia	Not available for widespread use - only if research protocol in place.
Primary ciliary dyskinesia	Currently available device is NOT FDA-approved and can be funded only through research endowment. Nasal probe not suitable for very young infants and children. Alternatives are nasal ciliary brush biopsy--not consistently reliable in terms of local pathologists' skills. Genetic sequencing still expensive.
Primary ciliary dyskinesia	Already discussed limitations of nasal nitric oxide. We also use biopsies and genetic testing.
Primary ciliary dyskinesia	The test is invasive, usually ENT performs a nasal or sinus biopsy. The specimen needs to be handled appropriately for preparation for electron microscopy. Both the biopsy and electron microscopy are done at a significant expense. The interpretation is difficult and not standardized or performed by an experienced reader.
Primary hyperoxalosis	Time to send samples to special lab and await results. Insurance barriers to testing and follow up measurement.
Primary immunodeficiency diseases	Expensive and takes long time to get the results.
Progressive supranuclear palsy	I use MRI to assess for the hummingbird sign, but this is not sensitive in most cases, particularly early in the disease.
Prolonged persistent pulmonary hypertension	After all therapies are exhausted, we seek genetic testing to determine cause, as in a recent case with twin who both died of the same disease and were unresponsive to all known medical therapy.
Pulmonary alveolar proteinosis	The single laboratory associated with measuring GMCSF autoantibodies for autoimmune PAP is not sufficient for the entire US. A better test would also diagnose the occupational (silica exposure) related PAP through serum testing.
Pulmonary alveolar proteinosis	Only available on research protocol.

Disease Name	Limitations to Current Diagnostic Devices
Pulmonary alveolar proteinosis	Limited availability and not FDA or CAP/CLEA approved. Not specific.
Pulmonary alveolar proteinosis	It is a send-out only and requires FedEx and special paperwork and lots of time.
Pulmonary alveolar proteinosis (autoimmune)	The only test available is part of a research study to which the patient must consent to participate.
Pulmonary atresia with VSD and multiple aortopulmonary collateral arteries	No one modality provides sufficient anatomic and physiologic information for interventional planning.
Pulmonary hypertension	We used echos, which can be nonspecific; cath or biopsy is more invasive and would like to diagnose pulmonary hypertension in a less invasive manner.
Pulmonary hypertension	Invasive, time-consuming, non-specific.
Pulmonary hypertension	ECHOcardiography is very nonspecific, not sensitive and detects late findings. Cardiac cath/angio too invasive for ongoing surveillance.
Pulmonary Langerhans cell histiocytosis	Invasive procedure.
Rare brain tumors	The current technology has some difficulty in distinguishing normal brain from tumor. Also, it is difficult to determine using current technology whether a tumor is rapidly growing.
Rare genetic malabsorption disorders	The devises and tests used to diagnose these disorders are still very subject to interpretation.
Rare kidney stone and mineral metabolism disorders	There is no unified approach to diagnosis; as it stands now, there is a lot of trial-and-error and guess work. A unified panel would provide an efficient, cost-effective approach to children (and adults) suspected of having rare kidney stone disorders.
Rare tumors, such as chondrosarcoma or minor salivary gland cancers	Too invasive.
Reflex sympathetic dystrophy	See above paragraph. These tests are nonspecific and provide little evidence of function of the autonomic nervous system.
Respiratory disorders related to underlying systemic autoimmune inflammatory disorders: e.g., LIP, NSIP, COP	Not specific. Invasive with risks. Many patients are too ill to tolerate surgical lung biopsy.
Respiratory failure in the newborn	Need for frequent blood gases invasively very problematic. No way to adjust oxygen automatically—all manual.
Retinitis pigmentosa	ERG. Genetic testing.
Retinopathy of prematurity	The infants suffer from the bright light of indirect ophthalmoscope and squirm. It is not easy to document from indirect view. Current camera requires touching the eye and use of bright visible light. None of these methods (indirect or fundus camera) can visualize swelling of retina, optic nerve elevation, absence of layers, delay in tissue development, macular edema, or retinal schisis versus detachment. All of those findings, determined by optical coherence tomography, are routinely used in the diagnosis of adult disease.

Disease Name	Limitations to Current Diagnostic Devices
Rett syndrome	Too expensive.
Sarcoma	Histology limitations with respect to assessing prognosis. Imaging tools don't always well demonstrate extent of tumor. Higher definition would facilitate surgical planning.
Sarcomas	Each new molecular or cytogenetic test specific for sarcomas has had direct effect on correctly diagnosing and treating sarcoma patients.
Severe combined immunodeficiency	Insurance approval.
Severe epilepsy of infancy	Routine EEG.
Sickle cell anemia	Slow and allows for doubt of provider about legitimacy of the patients complaint.
Sickle cell disease	Need to draw blood and send it to the lab.
Sickle cell disease	Low sensitivity.
Sickle cell disease	Again, not the diagnosis of the disease, though the electrophoresis takes time, but the manner by which we diagnose the presence of infection. Current culture tests take time, and at present, we do not have a reliably sensitive and specific laboratory test for infection. This forces us to overtreat.
Sjogren syndrome	These tests are not sensitive enough.
Sjorgren syndrome	The current available serological tests are somewhat non-specific and not confirmatory of the condition.
Skeletal dysplasias	Needs DNA testing (which requires insurance approval) and there are many genes to screen.
Smith-Lemli-Opitz syndrome	FDA is trying to regulate lab developed tests; this could make access to diagnostic testing challenging. Biochemical testing for SLOS requires use of sophisticated GC/MS instrumentation, not widely available.
Soft tissue sarcomas	Nonspecific imaging appearances; sarcomas responding to treatment may appear not to be.
Sphincter of Oddi dysfunction	Secretin-EUS, secretin-MRCP, ERCP-manometry, LFTs/amylase/lipase/+-biliary HIDA.
Spinal muscular atrophy	Applied for diagnostics at a symptomatic stage.
Spinocerebellar ataxia	Over 30% nationally and in our clinic over 60% of patient with clinically diagnosed spinocerebellar ataxia are negative on genetic testing with commercially available specific tests. Running full panels of specific genetic tests is very expensive.
Sturge-Weber syndrome	Often MRI of the brain with contrast and standard available sequences misses brain involvement in newborns.
Surfactant protein deficiencies	Genetic testing has delayed turn around, may miss more rare forms.
Syndromic craniosynostosis	They are expensive, require a blood draw (from infants which is difficult) and take a long time for results to return.
Takayasu's arteritis	I utilize a combination of physical exam and imaging (CTA, MRA, PET) for the diagnosis (and follow-up) of Takayasu's arteritis.

Disease Name	Limitations to Current Diagnostic Devices
Takayasu's arteritis—tests to assess disease activity	Generally, MRA is used, which can have nonspecific findings.
The porphyrias	Currently, the turnaround time is far too long. Test for urinary PBG needs to be available stat--results reported within 30-60 minutes, so that patients can be diagnosed and treated when they present with acute attacks.
Transverse vaginal septum	Ultrasound and MRI are limited in ability to visualize vaginal structures in children.
TTP	Turnaround time is the biggest hurdle.
Tuberous sclerosis complex	MRI and genetic testing are routinely used to make diagnosis. Genetic testing does not detect mosaics and low-level copy number mutations. MRI identifies lesions to confirm diagnosis but lacks ability to differentiate benign from problematic ones.
Type 2 endometrial cancer	Pipelle endometrial aspiration device.
Unknown diagnosis so need whole exome sequencing	VUS.
Urea cycle defects	Blood ammonia. Blood amino acids. Sequencing.
Urea cycle disorders	Take too much time to return to be able to institute therapies right away.
Urine creatine metabolism disorders	Cannot be done as part of standard newborn screening.
Uveitides	The sensitivity and specificity are limited.
Variety of pediatric oncology disorders	The gold standard (cultures) requires a fair amount of time before the result is known. We are then compelled to initiate treatment, medications, and admission for otherwise well-appearing (it makes sense, of course, to treat ill-appearing children) febrile children with fever and neutropenia. For those children without serious infections (the vast majority) we can avoid the morbidity associated with empiric treatment.
Various forms of vasculitis	Some tests are only specific for some forms of vasculitis (e.g., ANCA testing). Many tests are non-specific (e.g., acute phase reactants, other common lab tests).
Very long chain acyl coA dehydrogenase deficiency	Not FDA removed. FDA could take the test off the market if they wished.
Viral infections of the CNS, particularly in immune-suppressed patients	Need an FDA approved and commercially available test for such pathogen testing.

APPENDIX H: LIMITATIONS TO CURRENT THERAPEUTIC DEVICES

Disease Name	Limitations to Current Therapeutic Devices
Acute cardiopulmonary failure in children (necessitating mechanical support like ECMO/VAD/etc.)	No standardization between ECMO setups between different centers. Failure modes are often catastrophic, with little redundancy. There is an increasing literature on using systems engineering techniques to improve the safety and efficacy of this complicated system of systems.
Acute renal failure in children	There is no FDA-approved device for children to provide continuous renal replacement therapy (CRRT). Despite this, CRRT is the most commonly used method of kidney support used in pediatric ICUs. Existing devices approved for use in adult devices have too large an extracorporeal volume and are highly inaccurate with fluid balance when used in children. This leads to increased use of blood products, and problems with severe dehydration and shock when used in children.
Amyotrophic lateral sclerosis (ALS)	Unclear efficacy.
Amyotrophic lateral sclerosis	Available alternative communication devices are too slow; power wheelchairs are too large and heavy, and interfaces for noninvasive ventilation are uncomfortable for some patients.
Aniridia	Treat symptoms, don't cure the problem.
Aniridia	They scar and destroy heathy tissue (the treatments for glaucoma). There is no treatment for the fact that they are missing as iris and the artificial iris is not available in the US for some reason.
Anterior chest wall deficiency syndromes	VEPTR—not practical if absent support proximal or distal anterior chest.
Aortitis	Stents.
Atrial septal defect	The USA available ASD closure devices are metal based and remain in the heart permanently. It would be preferable for the device to degrade after the device has been well endothelialized.
Atypical HUS	Very expensive (Soliris).
Autoimmune encephalitis, e.g., anti-NMDAR Ab	Side effects, expensive, slow to work.
Autoimmune pulmonary alveolar proteinosis	High-efficiency, ultrasonic mesh-type nebulizer.
Autoimmune pulmonary alveolar proteinosis	Whole lung lavage, anti-sputum drug, oxygen therapy.
Autosomal recessive polycystic kidney disease (ARPKD)	Problems with angiotensin converting enzyme inhibitors include a temporary decrease in kidney function and hyperkalemia.
Avascular necrosis	Requires replacement of joint.
Bone cancers (osteosarcoma, lymphoma)	Invasive.
Cardiac sarcoid	Frequent ICD shocks.
Cardiac structural deficiencies (e.g., HLHS)	VAD's and mechanical total replacement hearts are short-term solutions relying on ultimate conversion to transplant pathway.

Disease Name	Limitations to Current Therapeutic Devices
CDKL5 encephalopathy	A variety of AEDs and VNS, which are approved for epilepsy from any cause.
Cervical dystonia	DBS is an invasive technique that may provide benefit but has complications and is not an ideal approach.
Charcot-Marie-Tooth disease	Orthosis that would have the ability to replace muscles that are too weak to function.
Chronic graft-versus-host disease	Only marginally efficacious and require a significant time commitment from patients.
Combined immunodeficiencies	Bone marrow transplantation is the only known cure for most combined immunodeficiencies. Because of the high morbidity associated with this procedure, only the most severely affected people are transplanted. It is supportive care for most other children.
Congenital cardiac valve disease	All but one valve device (Contegra) are FDA-approved only for adults. They are used off-label in pediatric applications. Homograft valves are really tissue transplants and are grandfathered. Mechanical valves require coumadin and bioprosthetic valves lack durability. Homograft valves are the only biological valve (i.e., not glutaraldehyde cross-linked) choice but are immunogenic (donor cells) and pro-inflammatory with limited durability due to accelerated calcific degradation, and lack growth potential as they become non-viable and acellular.
Congenital diaphragmatic hernia	They are invasive and our ECMO machine requires anticoagulation and ligation of cervical blood vessels.
Congenital diaphragmatic hernia	Patches, either synthetic or decellularized.
Congenital diaphragmatic hernia	Anti-coagulation may be necessary for paracorporeal lung device.
Congenital dilated cardiomyopathy	Size prevents use in very young patients; large size is a challenge is young patients.
Congenital disorders of glycosylation	Most subtypes of CDGs do not have available therapies.
Congenital glaucoma	They scar and fail.
Congenital heart disease associated with aortic coarctation of aorta or pulmonary artery stenosis	Bare metal stents approved for coronary and peripheral vascular disease are used to treat this condition right now. They are not optimal due to their permanent restriction on growth and inability to be dilated in a growing vessel.
Congenital heart disease	Biodegradable scaffolds for congenital heart disease patients are not available.
Congenital heart disease	[Congenital heart disease patients require better mechanical circulatory support.] They are too large and are designed for left ventricular support.
Congenital heart disease	Early, accurate intrauterine diagnosis and treatment. Insufficient imaging to identify defects early enough, and instrumentation and techniques to intervene early enough in fetal life to make a major difference.
Congenital hydrocephalus	Frequent failures for inserted shunts (CSF diversion devices).
Congenital micrognathia with airway obstruction	They are large (compared to a newborn baby), they can only activate in one vector (need multiple vectors), they stick out through the skin (activator pins), pin sites can become infected (in my practice about 10% of the time).

Disease Name	Limitations to Current Therapeutic Devices
Congenital peripheral pulmonary artery stenosis	Balloon dilation, cutting balloon dilation and/or stenting of peripheral pulmonary artery stenosis often only provides small improvements in pulmonary artery size over the course of multiple catheterization procedures.
Corneal ectasia (post-refractive surgery, keratoconus, pellucid marginal degeneration)	Contact lenses and corneal transplantation are current treatments for ectasia. Contacts do not halt progression of disease and do not always work. Transplantation is a major surgical intervention that is costly, takes months for recovery, and has significantly greater risks than collagen crosslinking.
Corneal stormal and anterior basement membrane dystrophies	Scarring or infection can occur with this treatment but in my experience, these are rare, especially with modern lasers.
Cowden syndrome	Not preventative.
Cystic fibrosis	For the fetus, I use diagnostic ultrasound imaging – it can only show us the complication once it has manifested (fetal bowel obstructions); it would be preferable to have tissue ID techniques or applications that are superimposed on the imaging to monitor the normality of tissue of detect changes that can progress to complications.
Cystic fibrosis	Vest - helps mobilize mucus through high frequency chest wall mobilization.
Cystic fibrosis	Nebulizers and drug delivery devices are not optimal—reach only parts of the lung and hit large airways.
Cystic fibrosis	Minimal effectiveness.
Cystic fibrosis	Lack of knowledge and lack of technology.
Cystic fibrosis	Current CFTR modulator therapies (ivacaftor, lumacaftor) are approved for the more common CFTR mutations (F508del, G551D, R117H). But getting them studied and approved in CF persons with rare mutations will be exceedingly difficult. We need biomarkers to track drug safety and efficacy in these patients.
Cystic fibrosis	All current therapies are palliative.
Cystinosis	Side effects of treatment with cystine-lowering agents are common and include gastrointestinal problems, frequent dosing, and a foul odor to the subject.
Deep Vein Thrombosis and Pulmonary Embolism (DVT/PE) in children	Limits in venous access and distort existing vena cavas.
Desmoid tumors	Cryoablation.
Perimembranous VSD	[Devices for closure of perimembranous VSD] are not designed or approved for this indication.
Preemie PDA	The current available devices available to close preemie PDAs are not designed for or approved for this indication.
Duchenne muscular dystrophy	Ultimately, does not treat the underlying systemic muscular involvement.
Dystonia	They are cumbersome, and they work only in a subpopulation. Predicting which cases will respond is difficult.
Dystonia	Not approved in labelling. HDE versus full approval creates an onerous amount of paperwork.

Disease Name	Limitations to Current Therapeutic Devices
Dystonia	I did that in previous question. Need better leads, programming, and the ability to use rechargeable batteries.
Early onset scoliosis	Size does not match patient often.
Early onset scoliosis	Most growing gross require surgical lengthening, and some are FDA off label.
Ebstein's anomaly	Poor residual valve function.
Endovascular flow diverters for intracranial use	Requires two anti-platelet agents, too many rebleeds, and thrombotic complications.
Eosinophilic esophagitis	Topical acting corticosteroids inhaled in Asthma are off-label used by swallowing the compound.
Eosinophilic esophagitis	Not FDA approved. Insurance coverage can be difficult. Side effects, intolerance.
Eosinophilic esophagitis and eosinophilic gastrointestinal disorders (in general)	Same as for diagnosis. Endoscopy and anesthesia.
Esophageal adenocarcinoma	Surgery and radiofrequency ablation are currently used. Surgery is morbid, and radiofrequency ablation is only effective in very early stage disease.
Familial LCAT deficiency	Only treats symptoms, not route cause.
Familial spastic paraplegia	Adding an unavailable drug to an available drug pump.
Focal dystonia	Don't work as well as needed.
Uncommon diseases	For a number of uncommon diseases, apheresis is the treatment of choice. Getting new apheresis machines approved for all the indications has been very slow. New machines are cheaper and easier to maintain and obtain kits to use.
Generalized dystonia	Surgical complications (infection in particular). Battery life. Adjustments of pacemaker. Need to accommodate a child growing into adulthood.
Genetic disorders of surfactant metabolism in newborn infants	Limitations include need for anti-coagulation.
Glycogen storage disorder type 1a/1b	Hand-held glucometers do not allow for continuous measurement. Current continuous glucose monitors have a lot of false positives for lows.
Graft vs. host disease	Need for access, not available everywhere, logistical challenges including reimbursement issues.
Granular corneal dystrophy	Only good for superficial disease, painful.
Heart failure in small children	Morbidity!!!
Heart failure with preserved ejection fraction	Poor outcomes with currently available technology.
Hereditary Hemorrhagic Telangiectasia (HHT)	Currently, AVMS are treated with embolization. The weaknesses of embolization include recanalization of the artery, new arteries forming after embolization, stroke during the procedure, or loss of embolic coil resulting in injury to the patient.
Heritable pulmonary arterial hypertension	Insufficient flow rates of portable oxygen concentrators particularly demand circuits.

Disease Name	Limitations to Current Therapeutic Devices
Heterotopic ossification of wounds	The devices, again, depending upon the patient and condition of the wound, we can use current lithotripsy technology to break up very dense heterotopic ossification of wounds. This often produces pain and is not optimal therapy.
Huntington's chorea	Ineffective.
Hyperammonemia	Hemodialysis is not currently extremely effective, only partially.
Hypertrophic obstructive cardiomyopathy	The balloons are not made for being placed in the septal perforator artery.
Idiopathic intracranial hypertension	Difficult to insert in the morbidly obese. High failure (5-year half-life) and infection rates (3–5 times nonimplant infection rates)
Idiopathic pulmonary fibrosis	No insurance coverage.
Idiopathic pulmonary fibrosis	Ineffective.
Idiopathic pulmonary fibrosis	Bulky, costly, doesn't deliver enough oxygen, runs out quickly.
Implantable artificial organs	VAD, Berlin Heart.
Internal carotid artery aneurysms warranting parent vessel sacrifice	When the patient can tolerate sacrifice of the artery, multiple approved/repurposed devices are typically necessary before a satisfactory artery occlusion can be achieved. In cases in which reconstruction of the artery is attempted by means of a flow diverting stent - such as when toleration of sacrifice is unlikely, multiple devices may still be necessary, unsatisfactory occlusion of the aneurysm, significant device related complications, and lifelong adjuvant medical therapy may be the outcomes.
Internal carotid artery dissection with associated symptomatic stenosis	Because the high radial force of a stent designed for atherosclerotic disease is not necessary, I have successfully used the low profile and quite flexible neuroform stent. Neuroform stent limitations for this application are: HDE status; maximal native ICA diameter cannot exceed 4.75mm; and a less than desirable flexibility at the stent termini.
Isolated, idiopathic dystonia	Not sufficiently effective for most types of isolated, idiopathic dystonia. Better understanding of brain targets and networks for deep brain stimulation. Better understanding of disease pathogenesis to develop disease modifying or symptomatic treatments.
Jeune	Expands only central part of chest, must be expanded by repetitive minor surgery.
Keratoconus	Contact lenses can mask the irregular astigmatism of keratoconus and improve vision but does not arrest the pathologic process. The patients are often uncomfortable and have compromised image quality.
Large congenital nevus	Multiple surgeries, multiple scars. Difficult post-op course.
Large thermal burns 60% TBSA	Integra is only the dermal replacement layer--after application of Integra, there is still a need for split-thickness autografting. Plus, the Integra is not resistant to infection.
Larsen's syndrome	Surgical complexity with poor joint function.
Laryngeal dystonia	Treatments are directed at symptoms and not disease.

Disease Name	Limitations to Current Therapeutic Devices
Lennox-Gastaut syndrome	Recently, Medicare has stopped coverage for vagus nerve stimulation for Lennox-Gastaut syndrome, which is a huge challenge for patients. Note that there is very good data in the literature for the utility of VNS for LGS, but not FDA approval.
Lesch-Nyhan disease	The size of existing devices is a bit too large for the pediatric population.
Leukodystrophies, with the exception of adrenoleukodystrophies	Brain MRI: lack of interest of neurologists and neuroradiologists. High cost of existing tests.
Limb ischemia without surgical or percutaneous options	Part of laborious clinical trials.
Lipomyelomeningocele	Existing materials for duroplasty (reconstruction of dura) as well as primary dural closure are all prone to local arachnoid scar formation and retethering.
Long gap esophageal atresia	Unreliable.
Long QT syndrome	Treat arrhythmias but do not prevent them.
Long QT syndrome	I'm unsure what the indications are for ICDs for LQTS, but in some rare cases, an ICD is indicated. improvements in device implant techniques and configuration would reduce barriers to using ICDs in younger patients in particular
Lung failure in newborn and children	Implantable.
Lymphangioleiomyomatosis (LAM)	Too expensive.
Lymphangioleiomyomatosis	Sirolimus slows progression but does not cure and only works as long as it being taken. Other supportive therapies such as oxygen, rehab, and transplant may be needed but are non-specific and have many limitations.
Lymphangioleiomyomatosis	Supportive care only.
Lymphangioleiomyomatosis	Limited benefit.
Lymphangioleiomyomatosis	Insufficient flow rates of portable oxygen concentrators particularly demand circuits. Lack of associated oximetry monitoring of SpO2 for activity.
Lymphangioleiomyomatosis	Expensive, many side effects, and not curative.
Lymphangioleiomyomatosis	Take some medicine. Medicine such as sirolimus has some adverse effects.
Lymphangioleiomyomatosis	Cumbersome.
Melanoma	Require surgery and extent of surgery required remains uncertain.
Membranous ventricular septal defects	Suitable only for a small number of defects because of rim requirements.
Mitochondrial disorders	Vitamin and supplement cofactors have had little proven effect. Treatment is symptomatic and supportive.
Mitochondrial disorders	They have no proven efficacy.
Mitochondrial disorders	Devices such as crutches or AFOs are simple and nonspecific and need to be replaced as an affected child grows. An adjustable device would be less expensive and adapt to changes in the child's physical disability that may progress over time.

Disease Name	Limitations to Current Therapeutic Devices
Moderate and severe pediatric traumatic brain injury	Most devices designed for adults without specific pediatric physical and developmental considerations.
More transcatheter valve options for congenital patients (smaller sizes)	Delivery systems are still too large, but this can be overcome by hybrid surgical approach. Use valves approved for pulmonary position in other locations (mitral, aortic, tricuspid). Not made for them, but can be used effectively.
Mucopolysaccharidoses (newborn screen)	Enzyme replacement therapy cannot reverse completely symptoms once they appear. Bone marrow replacement done later after symptoms appear is also not completely effective. Early identification is needed.
Mucus membrane pemphigoid	Systemically toxic drugs.
Multiple forms of dwarfism	For many small patients, existing implants (total hip, total knee) are simply too bulky and too big to fit.
Multiple myeloma	Ozurdex implant is not FDA approved for this indication, therefore not paid by insurance and extremely expensive.
Multiple myeloma	It's palliative only.
Multiple myeloma	For spinal instrumentation, the bones are often too diseased to use them effectively.
Multiple myeloma	Eventually cease to be effective.
Multiple myeloma	Bone marrow biopsies. Ablation of bone lesions. Cementoplasty.
Muscular dystrophies and spinal muscular atrophies	Ambulation supports, limb guards, wheel chairs, etc.
Neonatal hemodialysis machine	PD - limited by patient size. CRT - limited by patient size. Conventional HD - limited by patient size.
Neonatal kidney disease	Size and necessary blood volume are the major limitations.
Neonatal renal failure	Peritoneal dialysis is achievable with modified equipment for children. Smaller tubes and equipment would make it easier and safer to do.
Nephrotic syndrome	They have variable efficacy and many side effects.
Nephrotic syndrome and glomerulonephritis	We need therapies that directly address the mechanisms underlying these disorders. Our current therapies are non-specific and have considerable side effects.
Neurodegeneration with brain iron accumulation	Battery life is short, implanted device is prone to infection in children with debilitating dystonia.
Neurofibromatosis type 2	Cochlear implants cannot always be used to mitigate deafness in nf2. Brainstem implants yield poor hearing outcomes.
Neuroleptic malignant syndrome	ECT can work for NMS but is not always effective.
Non-ketotic hyperglycinemia	Portability.
Normal pressure hydrocephalus	High rates of malfunction and infection. Incomplete relief of symptoms.
Obstructed hemivagina with ipsilateral renal agenesis	Vaginal dilators—rigid, to prevent and treat vaginal stenosis and restenosis after surgery to relieve obstruction.

Disease Name	Limitations to Current Therapeutic Devices
OCD	Reimbursement. Target refinement. Biomarkers for appropriate patient selection.
Ocular chemical burns	Poor retention, glaucoma with present keratoprosthesis.
Orthopedic problems associated with acromegaly	Current devices are too stiff and not available in distorted sizes.
Osteogenesis imperfecta	Not sized correctly, not readily adaptable to abnormal anatomy or physical characteristics of the bone. Needs drugs if possible to prevent the loss of bone strength.
Osteogenesis imperfecta	People with OI keep breaking their bones. The hardware may be too stiff or the bone grows as the hardware stays in place, the multiple fractures makes it difficult to use an intramedullary device.
Pancreas cancer	We place metal stents in the biliary tree to relieve obstruction caused by pancreas cancer to ameliorate jaundice and allow the patient to get full dose chemotherapy if they are nonoperative. These stents can get clogged due to tumor ingrowth, and patients can develop cholangitis, a life-threatening infection. Patency tends to be no more than 3–6 months.
Pancreas cancer	Incomplete embolization of liver metastases. Incomplete ablation of pancreatic masses.
Pancreatic cancer	Major surgery, such as Whipple procedure, too often needed. Has major morbidity, mortality.
Pancreatic cancer	For the most part, these are invasive and surgery or endoscopy is required. Resection or bypass are often only palliative and carry morbidity and lengthy recovery in patients with limited life expectancy.
Pediatric acute kidney injury	Limitations due to small size of pediatric patients.
Pediatric cardiomyopathy	Use of ICDs in this population. The devices are large and smaller patients would certainly benefit from smaller devices. The subcutaneous ICDs are useful in avoid venous access, but are very large and difficult to use in pediatrics.
Pediatric congenital hydrocephalus	Shunts fail—highest failure rate of any implanted medical device. Success and safety of ETV and choroid plexus cauterization are dependent upon individual surgeon's skills. ETV stoma has a higher tendency for early closure in infants.
Pediatric congenital heart disease	Most of these devices that we are either engineered for an adult population and are either modified or used off label in the pediatric setting. Almost universally, the limitations of engineering for an adult population mean that the device provides substandard care in the pediatric population. This is broadly true, and applies whether you are talking about treatment with items such as heart valves, catheter-based technologies, ventricular assist devices, or diagnostic devices like echocardiography, cardiac catheterization procedures, etc.
Pediatric intractable epilepsy	Not approved; wrong size; developed for adult epilepsy which has different patterns; requires skull mount which is not feasible in young children.
Pediatric solid tumors	Need more clinical data. Need to improve size mismatch.

Disease Name	Limitations to Current Therapeutic Devices
Pediatric spinal dysraphism	Intraoperative monitoring for children with dysraphism can help protect nerve function, but devices are often designed for common adult problems and not for pediatric congenital problems, which often involve tiny nerve endings and affect strength and bowel/bladder function.
Pierre Robin Sequence	The current standard of care is tracheotomy or distraction. A better approach to this is needed.
Porphyria	Need for central line. Iron overload with prophylaxis repeated hematin infusions.
Porphyrias (all types)	Chronic hemin administration for acute porphyria treatment poses the risk for iron overload; it also takes 2–3 days before symptoms begin to be relieved. Afamelanotide therapy for EPP is currently not available in the United States. Treatment for PCT remains medieval (phlebotomy); the use of hydroxychloroquine or chloroquine takes several months before the skin symptoms begin to abate.
Primary ciliary dyskinesia	Treatment is currently supportive so not completely efficacious.
Primary ciliary dyskinesia	Therapeutic vest needs FDA approval.
Primary ciliary dyskinesia	Difficult to get insurance coverage for device without specific indication for primary ciliary dyskinesia. Other "general" devices are not as effective.
Primary ciliary dyskinesia	We suggest clearance devices like flutter or acapella valves.
Primary hyperoxalosis	Frequent dosing. Changes in requirements with growth.
Primary immunodeficiency diseases	Need a trained technical team to use the device to do cell selection.
Pulmonary alveolar proteinosis	The use of double lumen endotracheal tubes requires an anesthesiologist, two hours of OR time, and carries a high risk of respiratory failure.
Pulmonary alveolar proteinosis	Invasive, expensive, and not curative.
Pulmonary alveolar proteinosis	Bronchoscopy with whole lung lavage.
Pulmonary alveolar proteinosis (autoimmune)	Dose, timing, and duration are unknown.
Pulmonary hypertension	Stents in atrial septum. Not designed for atrial septum. It would be nice to have dog bone–shaped stent for this purpose.
Pulmonary hypertension	For secondary PHTN, oxygen and assisted ventilation—the oxygen is not necessarily too cumbersome, but assisted ventilation can significantly limit patient activity.
Pulmonary valve regurgitation	The current bioprosthetic surgical or catheter delivered valves are animal-derived heterografts or cadaver derviced homografts with limited lifespans, related to immunologically mediated degradation and/or simple wear.
Pure autonomic failure	Inadequate convenience to the patient.
Pyruvate dehydrogenase deficiency	Use so far not based on highest level evidence of safety/efficacy. No third-party payment possible, which is hardship for physicians and, especially, affected families.

Disease Name	Limitations to Current Therapeutic Devices
Rare brain tumors	Current MRI technology has some difficulty in distinguishing normal tissue from tumor tissue. Also MRI technology does not determine whether the tumor is growing rapidly or not.
Rare kidney stone and mineral metabolism disorders	The available therapies are "broad-spectrum" and do not precisely address underlying mechanisms.
Rare pediatric airway	Can't respond to growth, inaccurate sizing, migration, scar-inducing.
Rare pediatric craniofacial syndromes	The modifications we make are imperfect at best.
Respiratory failure in the newborn	Just use pulse oximeters—no way of assessing pH or pCO2.
Respiratory failure unresponsive to surfactant therapy	Currently, respiratory failure unresponsive to surfactant therapy is often treated with extracorporeal membrane oxygenation, prolonging the imminent outcome. Knowledge of specific entities that are not amenable to existing therapy and with an adverse outcome, may make decision making easier to not prolong therapy.
Restrictive cardiomyopathy	Does not resolve diastolic dysfunction. Difficulty with inflow into the pump, due to small ventricular cavity.
Rett syndrome	Does not meet the needs of all patients.
Rett and Rett-related disorders	They are just not available and insurance may not approve them.
Rett syndrome	Don't work very well.
Rett syndrome	Baclofen pumps, vagal nerve stimulation.
Right ventricular outflow tract dysfunction (pulmonary regurgitation)	These devices have relatively large, stiff delivery systems. They may not be appropriate for small children. Often difficult to advance to implant location.
ROHHAD syndrome	Portability and availability at home.
Sarcoma	Risk to adjacent structures for injury during resection.
Severe epilepsy of infancy	Vagal nerve stimulation is marginally effective.
Severe heart failure in children	Cannot be used in the smallest children. High stroke rate. Cannot be used in single ventricle hearts (most common etiology of severe heart failure).
Short QT syndrome	Can treat arrhythmias but not prevent them.
Sickle cell	Total hip and knee devices. No significant problems.
Sickle cell disease	Variable effectiveness of devices and medications in providing effective pain control. Optimal pain management without impacting mental status/level of alertness would be very desirable, might allow these children (and adults) to pursue activities of daily living, school, etc.
Sickle cell retinopathy	Retinal lasers.
Skeletal dysplasia	Devices too small.
Skeletal dysplasias	Fassier-Duval rods.
Sphincter of Oddi dysfunction	ERCP/sphincterotomy/??? Botox injection.
Spinal AVM	Most devices too large to gain optimal access to lesion.
Spinal muscular atrophy	Portability.

Disease Name	Limitations to Current Therapeutic Devices
Spinal muscular atrophy	Motorized wheelchair. Hoyer lift.
Stevens-Johnson syndrome	Poor efficacy of amniotic membrane transplant. Poor success of corneal transplant surgery or keratoprosthesis surgery.
Stevens-Johnson syndrome	Keratoprosthesis has poor outcome in Stevens-Johnson syndrome.
Sturge-Weber syndrome	VNS and related devices are non-specific. They help control the seizures but do not otherwise impact the syndrome.
Syndromic craniosynostosis	Require surgery to place plates and screws (currently they are dissolvable, which eliminates need to remove in the growing child). However, a new way to diagnose and insert a genome/receptor fix would obviate the need for surgery in the first place.
The porphyrias	Approve afamelanotide for use in treatment of erythropoietic protoporphyria [EPP]. Improve method for implanting afamelanotide under the skin.
Third-degree burns	The biggest hurdle is in skin grafting, as there are no devices/biologics/drugs that truly allow us to "expand" the limited skin of the patient.
Thrombotic thrombocytopenic purpura (TTP)	Use of plasma for a plasma exchange is expensive and exposing the patient to 30–40 different donor's blood. This is not ideal.
Tourette's syndrome	DBS.
Tracheobronchomalacia pediatric and adult	These devices need to go through regulatory approval. Such devices should be able to be 3D printed in a hospital setting available to all qualified physicians.
Transcatheter ASD device (cardiac)	Risk of erosions. Few choices in device design/size.
Transplantation	Artificial heart, lung, liver.
Transverse vaginal septum	Currently, mostly using riding vaginal dilators to relieve vaginal stenosis after it occurs.
Type A carotid cavernous fistula	Multiple devices such as detachable coils must be used to close the CCF from within the cavernous sinus. The parent vessel may ultimately have to be sacrificed. Often the ICA caliber will be too large to accommodate a flow diverting stent. Use of other devices such as Onyx 34 adds to treatment complexity and increases risk to the patient.
Variety of pediatric oncology disorders	In addition to indwelling vascular access devices, it would be to have noninvasive technology for diagnosis and treatment.
Vascular obstructions in children	Limited redilation potential, lack of flexibility.

APPENDIX I: CHALLENGES WITH DIAGNOSING AND TREATING PEDIATRIC RARE DISEASE PATIENTS

Please briefly describe (in two to three sentences) any challenges you have faced in treating or diagnosing rare diseases in patients who are 21 years or younger.
1. Lack of knowledge of the clinical presentation/natural history. 2. Coverage of genetic testing by insurance companies.
1. My ignorance in general about how to navigate the vast institutional and federal resources. 2. Lack of protected time for clinical research.
Ability to use agents or tools available in the adult population in children. Also, limited interest in developing specific tools for children.
Access due to insurance problems.
Access to care (location—too far, insurance-—not covered, specialists—none in local area, denied by insurance). Funding from government and private sources.
Access to medical treatment facilities with resources for treatment and limited research funding for investigator-initiated research is still a problem. Knowledge of available resources, in some cases, is still very limited.
Access to medications/insurance issues. Ability to pay for diagnostic testing. Lack of treatment options.
Access; expense of devices.
Accessibility to expert diagnosis and care.
Additional IRB regulations.
Adequacy and expense of genetic testing (e.g., hereditary pancreatitis).
Adherence to therapy, uncertain readiness of adolescents to take control of their own care and inability to assess readiness.
Appropriate devices just not available. HDE limit of N = 4,000 way too small. Needs to be 12,000–20,000 to capture all the kids.
Assessing disease activity with respect to biologically relevant mediators. How to capture GI tissue.
Availability of rechargeable technology.
Because these patients are spread out among many centers across the U.S. (and world), it is hard to generate experience and data. This is why we need multi-centered registries and studies for rare diseases.
Better genetic testing.
Blood drawing from children under the age of 4.
Caught between the pediatric and adult worlds.
Challenges from lack of accessible devices.
Challenges I routinely have in diagnosing rare disease patients under 21 years of age include difficulties in getting insurance coverage for genetic testing and some drugs used off-label; limited availability of diagnostic tests for rare diseases; and lack of effective drugs or devices.

Please briefly describe (in two to three sentences) any challenges you have faced in treating or diagnosing rare diseases in patients who are 21 years or younger.
Communication is one of the largest impediments in the cognitively disabled individuals with rare genetic neurodevelopmental syndromes. Having a communication platform that can be quickly adapted and used for any child to ascertain the child's level of ability and to understand any other neurocognitive deficits would be a major advance.
Correct diagnosis. Profound weakness with severe disability. Complications of severe weakness.
Cost of diagnosis is a limitation. Availability to tests is second.
Costs of diagnosis. Lack of available tests for diagnosis. Poor insurance coverage for medical foods and necessary pharmacologic doses of supplements (amino acids, vitamins). Limited numbers of trained providers. Horrible expenses of newly developed agents effective in therapies. Frequent and repeated requests for prior authorizations.
Coverage for appropriate genetic tests, coverage for medical formulas, and high dose vitamin supplements.
Current methods are invasive and cause emotional distress in addition to being expensive.
Delay in diagnosis due to lack of knowledge amongst referring physicians.
Delayed diagnosis.
Delays in arriving to correct diagnosis creates many difficulties including allowing for progression of disease.
Delays in patient referral.
Devices not appropriately sized.
Devices not designed for/adapted to children; main barrier is cost to companies for development, and relatively small market. Because of this, even when devices exist (e.g., video for use during long MRI studies), they are very expensive so not prioritized by hospitals, even though globally they would save money by saving need for sedation/anesthesia and shortening time. Similar barriers exist for other devices or adaptations for children.
Devices not modifiable to patient size; expensive.
Diagnosing patients has been challenging due to costs of genetic testing.
Diagnosis and management.
Diagnostic challenges.
Diagnostic tests.
Difficulties in diagnosis.
Difficulty in funding genetic sequencing studies; frequent need to rely on invasive procedures such as bronchoscopy and bronchoalveolar lavage or lung biopsy; requirement for sedation/anesthesia and radiation exposure for serial lung CT scans.
Difficulty in planning for long-term care/prognostication for family/patient.
Difficulty with attending for tests due to concomitant disabilities and other commitments. Lack of interest in adolescents. Lack of resources for coordinated care—a big problem in Australia!
Disease heterogeneity.

Please briefly describe (in two to three sentences) any challenges you have faced in treating or diagnosing rare diseases in patients who are 21 years or younger.
Education and understanding HDE and financials with regard to reimbursement and third-party participation.
Emotional challenge of dealing with poor outcomes in young patient populations and their parents.
Expensive cost.
Expensive diagnostic tests that require discussion with hospital lab personnel.
Few treatment options geared for specific patient population and limited investment to develop new technologies.
Few treatments, access to testing (e.g., insurance), few clinical guidelines for managing rare disease.
Frustration of not being able to offer testing to most patients because they are not reimbursable by their insurance. Not being able to get parental testing. Frustration of often not having any treatment to offer once a diagnosis is made.
Funding for genetic testing.
Genetic testing.
Genetic testing early on.
Getting blood samples from entire family for full genetic analyses.
Getting testing covered. Getting meds covered.
Hard to find diagnostic devices.
Hard to stop the disease. For fractures that occur again and again in the same bone, it is difficult to get an appropriate implant.
Hesitancy in the culture of the medical field to diagnose with psychiatric or neuropsychological tools that they are unfamiliar with. Pediatric HD is easily diagnosed with standardized longitudinal assessment before the movement disorder is manifest. Most cases wait years in significant distress prior to receiving a diagnosis or treatment plan that is acceptable.
Huge diagnostic challenges lead to many delays in diagnosis and once diagnosed few treatments exist.
I am a geriatric psychiatrist so I am usually working with someone who has called me in as a specialist. This can be challenging because we are trying some things that are not approved, and I do not have a relationship with the family. Also ECT has a stigma attached.
I am a leader of a North American consortium focused on rare congenital heart disease. Government grants are very restricted and there is little interest by industry because the market is small.
I am a neonatologist. The biggest challenge is the cost of doing detailed genetic testing in infants with rare diseases like polycystic kidneys disease, central apnea, inborn errors of metabolism, cystic fibrosis, etc.
I am an adult hematologist, and rarely see individuals that are younger than 21. The few patients that I have are either young men with hemophilia, which has a lot of treatment (though IV access is very difficult) or young women with menorrhagia that is very difficult to control even with all of the options (factor replacement, anti-fibrinolytics, hormonal manipulation).
I am MSK radiologist. And we detect the lesion on imaging studies. But in many occasions, we lose the follow-up of these patients.
I consult in a major hospital on many different ages and conditions. With improving diagnostics, I see the therapeutics as a larger challenge for us. Many interventions remain supportive or are intensive (cardiac surgeries, devices) but not ideal, and usually are not innovative.
I have difficulty counseling patients in this age group because the scientific evidence often does not apply. Secondly, patients in this age group can be unreliable in their follow-up with providers.

Please briefly describe (in two to three sentences) any challenges you have faced in treating or diagnosing rare diseases in patients who are 21 years or younger.
I have more trouble treating older individuals.
I practice in a rural area and access to adequate testing is severely limited.
I'm not a pediatric neurologist. Patients who are under 21 that I see are no different than adults, except for minors, where parents may not want to make decisions for their children and want to wait—and waiting can make the problem worse.
In movement disorders, a lack of familiarity with the clinical features can lead to misdiagnosis. The expense of genetic testing has significantly limited our ability to make specific diagnosis in the dystonias and the ataxias.
Inability to obtain rhIGF-I for children with GH receptor deficiency.
Inadequate diagnostic (other than invasive) and limited treatment options.
Inadequate fund of knowledge and clinical exposure. Limited clinical trial options. More pediatric pulmonary diseases that do not typically survive to adulthood are getting increasingly seen, with very little previous training or exposure.
Inadequate knowledge regarding natural history of disease in attempting prognostication. Inadequate knowledge regarding pathogenesis of disease and associated lack of effective treatments.
Inappropriate behavior by insurance companies balking at paying for testing.
Inavailability or excessive cost to confirm or reject a rare diagnosis. Lack of adequate information on treatment and support of these subjects.
Institutional hurdles for adult internists also to see pediatric patients in clinics.
Insurance approval for testing.
Insurance barriers to payment. Identification of appropriate laboratory services for testing. Timing of testing in newborn or early infancy.
Insurance changes, problems with illness taking child out of school, cost of therapy/diagnosis.
Insurance coverage is the main problem. Medicare (CMS) is the source of much of this problem, as if they do not pay for a test, no one else feels they have the obligation to do so.
Insurance coverage, red tape.
Insurance reimbursement.
Invasive surgery, consent issues, family dynamics.
IRB hurdles, limited device availability.
It is difficult for patients/families to travel for expert consultation and there is not a reimbursable mechanism for 'remote' consultation. Insurance also poses constraints on having the appropriate testing done at an experienced facility. Limited noninvasive diagnostics are available and therapies are very limited.
It is difficult overcoming regulatory hurdles in this population.
It is difficult to keep up with the progress in tests for rare diseases because they are not in our literature or advertised/marketed as aggressively. Getting insurance companies to cover the cost of testing and treatment can also be difficult because these patients don't fit the usual payment screening criteria.

Please briefly describe (in two to three sentences) any challenges you have faced in treating or diagnosing rare diseases in patients who are 21 years or younger.
It is often hard to get a concrete diagnosis for some time. Once the diagnosis is reached, there can be difficulties related to breathing/airway and hearing. Due to a host of other issues, some of the primary respiratory and audiological concerns are not addressed until later.
It is very hard to accurately diagnose them. Typically there is a prolonged lag time before I see them due to difficulty in diagnosis. This results in severe organ damage to a substantial amount of patient before I see them, which severely complicates the possibility of bone marrow transplant.
Kernicterus is frequently caused by medical mismanagement, so the potential for legal action by the families makes many doctors reluctant to diagnose the condition, even though early diagnosis can make a huge difference in the future health and well-being of the child.
Lack of appropriately sized equipment, adaption of adult techniques to children.
Lack of approval, lack of appropriate sizing of devices that were developed for adults, and bureaucracy of HDE.
Lack of approved drugs for children.
Lack of availability of FDA-approved devices which have been used safely worldwide for many years contributes to lack of insurance coverage. Out-of-pocket expenses are prohibitive for patients, making treatment inaccessible.
Lack of computational pipelines for analysis of exome or whole genome data for discovery of candidate variants; lack of model systems for testing function of discovered variants and therapeutic strategies.
Lack of diagnostic test. No proven treatment.
Lack of evidence makes for very difficult conversations with parents.
Lack of funding.
Lack of genetic testing available that is covered by insurance. Need for anesthesia to do LPs for drug delivery because a port is not available.
Lack of genetic tests easily available.
Lack of growing conduits and valves.
Lack of outcome measures to assess disability or impairment in children
Lack of pediatric specific resources.
Lack of randomized data to establish efficacy for treatment of try new devices or therapies.
Lack of rapid, efficient methods for making specific, especially genetic, diagnoses.
Lack of sensitive and diagnostic tools. Lack of specific and targeted therapeutic approaches for rare diseases.
Lack of specific diagnostic tests and lack of prognostic biomarkers or biomarkers to facilitate assessment of response to therapy. Available devices for supportive care are useful but have limitations.
Lack of specific tests and therapies.
Lack of tests with powerful risk discrimination in diseases that have direct impact on eligibility for sport and military service.
Large medical records. Difficulty distinguishing primary symptoms from iatrogenic ones. Lack of familial access to DNA for genetic testing.
Limited access.
Limited availability of medications or safety information in children.
Limited data available for device use.

Please briefly describe (in two to three sentences) any challenges you have faced in treating or diagnosing rare diseases in patients who are 21 years or younger.
Limited diagnostic blood tests; limited treatment options; insurance constraints.
Limited diagnostics tests for prognosis. Limited devices available for treatment. Expertise usually confined to only a few centers. Limited natural history data.
Limited resources to cover the costs.
Limited skin.
Limited technology available and limitations of the one VAD technology that is available.
Limited therapeutic options. Heterogenious outcomes. Insurance barriers to coverage of meds, DME. Limited home RN.
Limited treatment options.
Logistics of travel to diagnostic/treatment centers. Incorrect diagnoses, resulting in poor medical treatment approach.
Making a diagnosis of PCD remains challenging. We need to be able to use nasal nitric oxide analyzers clinically and could use the FDA's help in this regard. And we need CFTR modulator therapies for all individuals with CF, not just those with the more common mutations.
Making the diagnosis. Treatment options.
Many of the advanced diagnostics that have been perfected for adult disease have limited versions for use in children. Because of the cost limitations, they are not likely to be further developed.
Many of them are inherited diseases.
Many potential tests not clinically available and use of research tests exposes provider and institution to liability.
More difficult to diagnose while in early stages of disease.
More difficult to do research in this age population that is critical for developing new diagnostic tests and therapies. Part of the difficulty is the rarity of the disorders.
Most have been misdiagnosed prior to being appropriately referred. Many have had inappropriate surgeries done when the condition wasn't recognized. The families have been given misinformation. In addition, the severe psychological challenges faced by these patients and their families are difficult to meet.
Most interventions if approved for adults, are not approved for pediatric population. Difficult to obtain approval in that patient population.
Most of these patients are very apprehensive and difficult to manage in a pediatric dental office setting.
Mostly in identifying the genotype.
Need for repeated endoscopy for disease surveillance associated with changes in the diet. Psychosocial effects of broad food elimination. This is exacerbated by the empiric elimination of foods that turn out not to trigger the disease.
Need to build patient specific devices for patients to address wide range of anatomy. Appropriate biocompatible and bioresorbable materials available for which to make devices.
New technology.

Please briefly describe (in two to three sentences) any challenges you have faced in treating or diagnosing rare diseases in patients who are 21 years or younger.
No challenges per se; rather would have preferred better means of diagnosis, monitoring, and/or intervention relative to maternal status in pregnancy or complications to the fetus. So, age was not a factor. Most patients were part of the Medicaid system.
No good tests available.
No specific treatment options are available.
No therapies available.
No treatment options offered.
No viable treatment.
Non-specific diagnostic testing. Multiple testing needing to be performed. Patient frustration with lack of answers.
Not all the causes of CMT are known. I am deeply engaged in whole exome sequencing to find these still unknown causes. We have been able to get adequate support for the sequencing itself, but the NIH has not adequately supported the bioinformatics platform (Genesis 2.0 based out of the University of Miami) that is needed to assemble and curate all of the variants such that the true causes can be found.
Not enough noninvasive tool.
Obtaining CSF or brain biopsy is a challenge.
Obtaining uncommonly available tests.
Often cost or the fact that it is not thought of in younger people.
Only experience is with juvenile Huntington's disease and main issue is phenotype is different—genetic test is helpful in this population.
Overlap in phenotypes, lack of a streamlined approach to genetic testing, high cost.
Parental stress creates an overbearing and paternalistic approach to disease management because of the need to learn and care for this disease without the patient being independent. This burden has been studied in only a few diseases such as CF, but is shared across rare diseases.
Parents have to take the children to many places to find an expert. Then after diagnosis trying to find a treatment. For those with genetic diseases finding a drug or a gene modification takes funds and time.
Patient expectation very high compared to evidence-based generated opportunities.
Payment for gene mutation analysis.
Pediatric guidance by FDA. Growth of child. Limited options.
Pediatric patients require special considerations for advanced imaging (e.g., young children need to be sedated for MRI or when undergoing biopsy). Some procedures can only be performed at certain hospital sites due to credentialing issues.
Pleomorphic phenotypes.
Poor healthcare system for caring for adults with rare metabolic diseases, especially during an acute crisis.
Poor outcomes.
Precise diagnosis—interpretation of VUS and no treatments for most of the conditions I treat.
Proper devices not available for pediatric patients.

Please briefly describe (in two to three sentences) any challenges you have faced in treating or diagnosing rare diseases in patients who are 21 years or younger.
Purely the complexities of pathophysiology in pediatric patients—untangling growth and development retardation.
Rapid ADAMTS13 levels ideally as a POC test would be very helpful.
Reimbursement, getting consent.
Reimbursement.
Repeated endoscopies for patients undergoing therapy for eosinophilic esophagitis or other eosinophilic gastrointestinal disorders.
Requirement for anesthesiology assistance for diagnostic testing or therapeutic intervention.
Restriction of Rx by insurers, denial of use of Rx modality.
Same as everyone else: limited access to testing, therapeutics that haven't changed in decades, limited information on efficacy of therapeutics, INSURANCE, INSURANCE, INSURANCE.
Size constraints. Invasive tools are ethically challenging (Lycox).
Size constraints—devices designed for adults don't fit in children.
Size of devices that can be used to help with symptoms.
Small children—size is an issue.
Small market.
Small market and thus lack of industry incentive to invest into R&D.
Small size of the patient.
Small-sized patients with high risk or discomfort associated with invasive tests or larger volume/repeated blood draws. Heterogeneous patient populations.
Smaller devices needed.
Some diagnostic tests may be invasive. There are not effective medicines to treat some rare diseases, such as BHD.
Somewhat less compliant than adults.
Special regulations/situations for pediatric populations (e.g., utilization of drugs [or devices?] that are not labeled/approved specifically for pediatrics and associated problems that arise from doing so). Invasive tests are harder to perform/defend on pediatric patients and, if sufficiently young, may incur increased risk as may need to be performed with sedation/anesthesia, while in an adult, it may be done without sedation/anesthesia.
Steady use of meteleptin in patient with Lipoatrophic DM by irregular follow-up by responsible adult.
Technical—miniaturization necessary.
The diagnosis is easy once they are in clinic and studied by physicians, scientific colleagues.
The early diagnosis of pancreas cancer is a major problem. Virtually all patients are incurable at the time of diagnosis.
The greatest challenges are failures that occur after surgery, which can amount to greater than 50% depending on the starting position of the meatus. Though parent expectations are tempered, the high failure rate is still demoralizing.
The greatest challenges have been related to obtaining insurance approvals for diagnoses and eventual therapeutic interventions.

Please briefly describe (in two to three sentences) any challenges you have faced in treating or diagnosing rare diseases in patients who are 21 years or younger.
The lack of knowledge about the etiology of limb deficiencies.
The lack of private insurance coverage.
The long life ahead where continued routine high risk surveillance or even timing of prophylactic surgery are issues (e.g., in heritable cancer syndromes).
The main limitation for diagnosing rare diseases in adults is resistance of payers to pay for testing. The main approach for diagnosis now is DNA sequencing.
The major challenge is to ensure that participants have access to the full range of therapies. This varies by region and school district. The specific issues related to these difficulties may or may not relate to adequate facilities.
The most common challenge is that the shape and size of the devices designed to treat a typical person are unusable due to size or shape differences. The following fall within this rubric: asymmetry (of limbs, face, head), atresia or stenosis (of ears, eyes, nose, mouth), contour deviations (due to masses, anomalies, surgery).
The patients I encounter are pregnant, which can be challenging in terms of diagnostic capabilities and treatment options.
The primary obstacles have been in understanding the mechanism or prognosis for the rare diseases which all have a phenotypic spectrum and it is very difficult early on to determine an individual patient's location on that spectrum.
The ready availability of affordable diagnostic testing is a major problem and treatments are either not available or ineffective.
The usual challenges in imaging the pediatric population. Concern for radiation and body habitus more difficult to image by CT or MR. Ultrasound is well-suited but limited by lack of FDA-approved contrast.
There is a lack of quality prospective trials. There are medications that have worked well in retrospective experiences but not FDA approved and so they are difficult to get covered.
There are limitations to the sensitivity and specificity of the available markers at this time.
There are no special challenges in terms of diagnosis, with the exception of newborns for which sample collection is a challenge. I am not an expert in treatment, for which I am sure there are many special challenges.
Transitioning from pediatric to adult medicine is challenging.
Unfortunately FDA approval of diagnostic genome technologies is very protracted and limited to a single supplier, which raises costs and creates barriers to health care access.
Unknown long-term effects of treatment options, uncertainty about natural history of diseases.
Vascular access, diagnostic studies, patient comfort, procedural sedation, and analgesia...
Waiting for 2 to 4 months to get the answer of these genetic mutation in immune deficiency diseases to determine what is the best line of a treatment for a given patient.
We don’t see that many of them. Mostly these patients have some form of dystonia. It is mainly a clinical diagnosis with only some genetic tests. A challenge is in distinguishing psychogenic dystonia.
We have had to do all of our specific diagnoses as part of clinical research under IRB-approved, clinical protocols designed to provide a “clinical research diagnosis”. This is cumbersome for everyone involved and not really practical. The only reason we are able to do it is that we couple this to our molecular pathogenesis-driven diagnostics and therapeutics development research program that is funded by NIH/NHLBI and NCATS-TRND.
We need the treatments available as outlined above.

Please briefly describe (in two to three sentences) any challenges you have faced in treating or diagnosing rare diseases in patients who are 21 years or younger.
We would like to diagnose earlier and have better and more specific treatments. We need to be able to better prevent neurologic deterioration.
When these patients become adults, they outgrow their mechanical devices. In the case of heart valves, many require a major operation to implant a valve. In many instances, this makes their subsequent heart transplant more difficult.
Worse insurance reimbursement.
Young people diagnosed with progressive blinding disorders have educational, social, and vocational challenges.

APPENDIX J: ACKNOWLEDGMENTS

The project working group would like to thank all of the survey participants for their time and contribution to this important project. We appreciate the help from coordinators and leaders of the FDA CDRH Advisory Committee, Pediatric Advisory Committee, Pediatric Device Consortia, and National Center for Advancing Translational Sciences/Office of Rare Diseases Research (NCATS/ORDR) Rare Diseases Clinical Research Network Program. We are grateful to the nine physicians who participated in the cognitive testing of the survey. We also thank the FDA Office of Planning for their guidance in the survey development and report. We appreciate the advice received from the participants of the project stakeholder meeting, including members of the American Academy of Pediatrics, American Medical Association, National Organization for Rare Disorders, and AdvaMed. We thank our contractor ICF for their survey expertise and commitment. Last, but not least, we thank our colleagues in the Office of Orphan Products Development (OOPD), both past and present, for their encouragement and excellent advice. This project was supported by funds from FDA OOPD and NCATS/ORDR.