Unmet Medical Device Needs
for Patients With Rare Diseases

NIH National Center for Advancing Translational Sciences

FDA U.S. FOOD & DRUG ADMINISTRATION

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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**

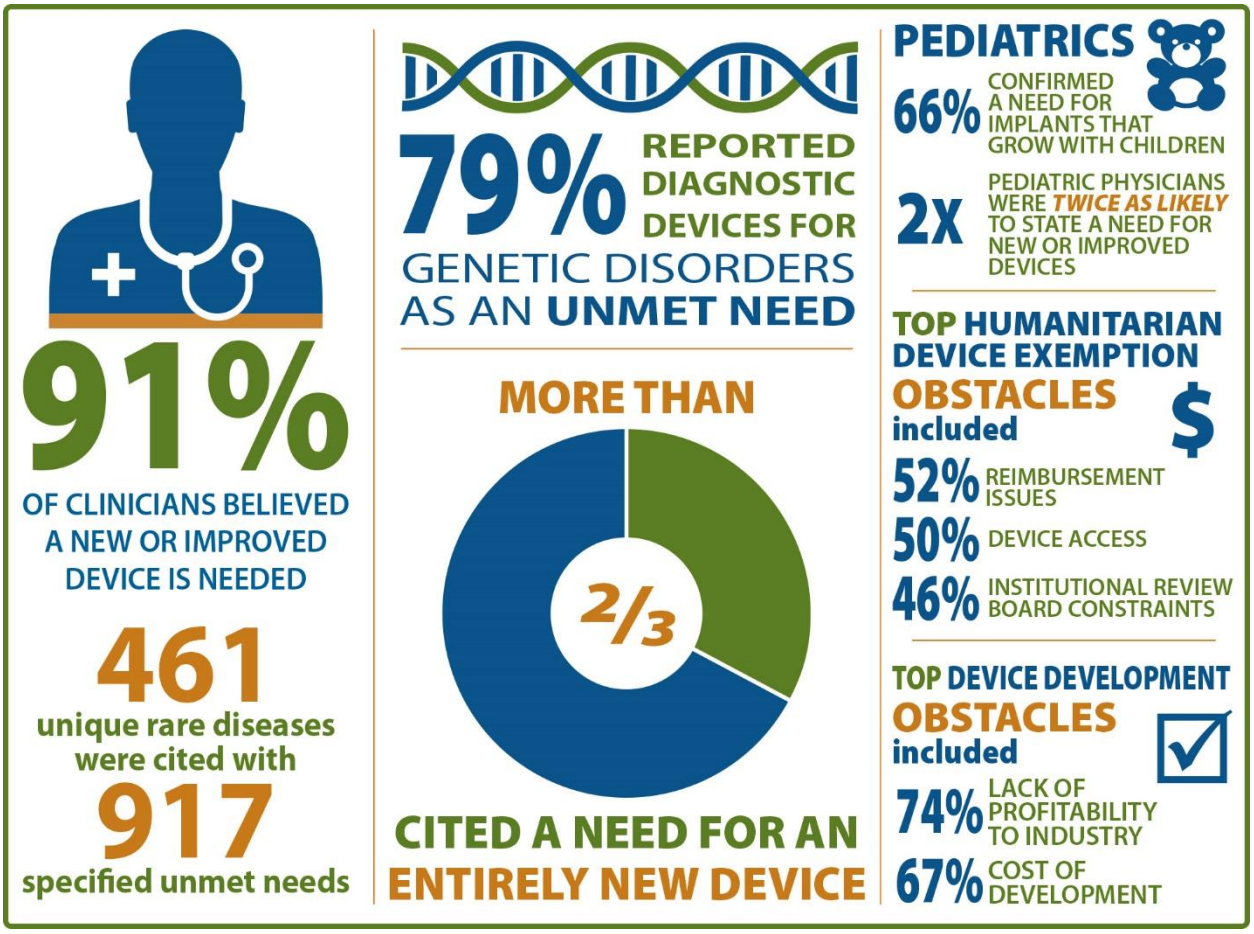
74% saw the lack of profitability to industry as a large impediment
67% saw the cost of development as a large impediment

- **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.

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[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.

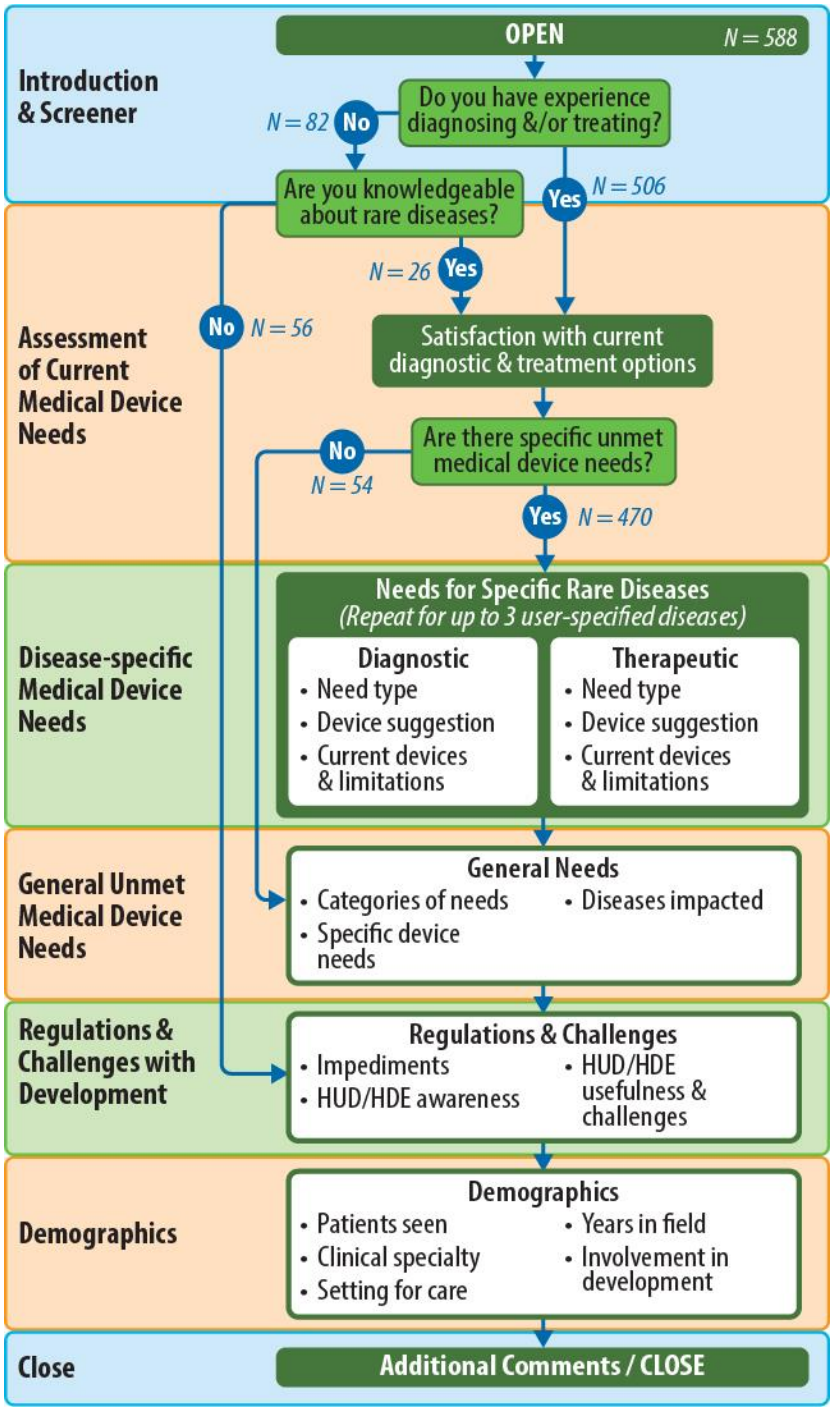
FDA and its contractor, ICF, independently sought and received Institutional Review Board (IRB) approval before fielding the survey. The FDA CDRH Advisory Committee survey opened Nov. 4, 2015, and closed Dec. 5, 2015. The FDA PAC, FDA PDC, and NCATS/ORDR RDCRN survey opened Jan. 28, 2016, and closed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

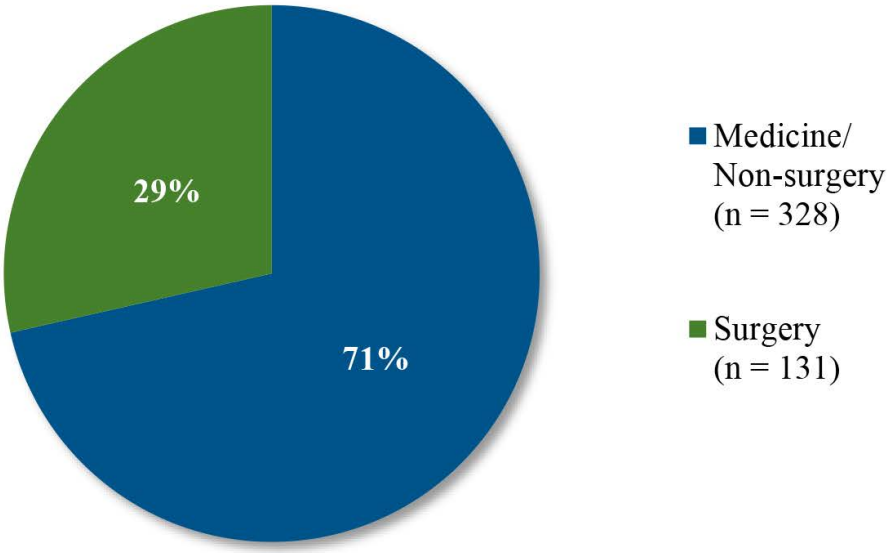


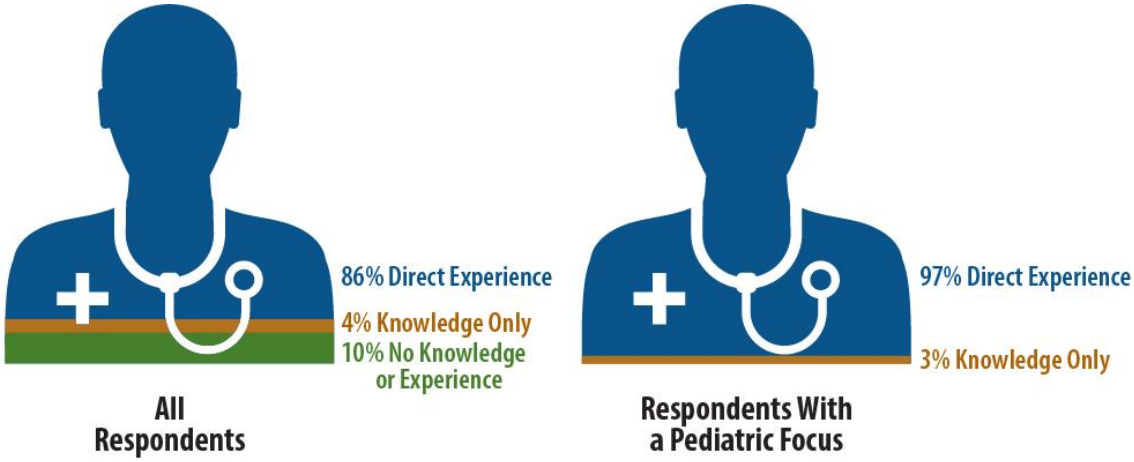
Table 1: Clinical Specialties of Respondents

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.

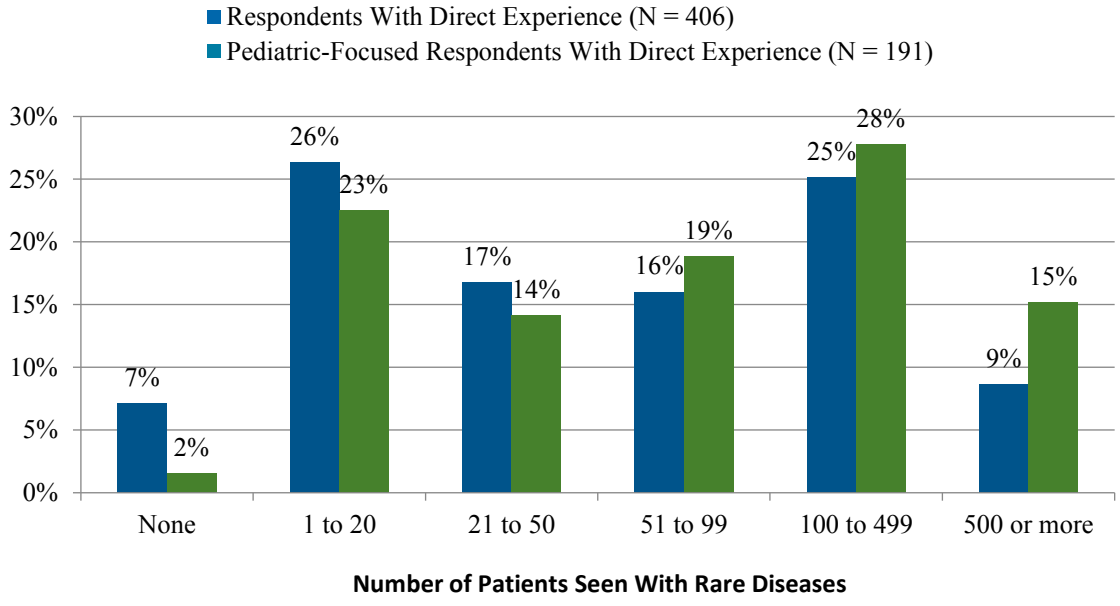
As Figure 3 shows, a large majority (86 percent) of the total respondents reported they had direct experience diagnosing or treating patients with rare diseases. The remaining respondents either had knowledge of rare diseases but no direct experience with rare disease patients (4 percent) or had neither 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

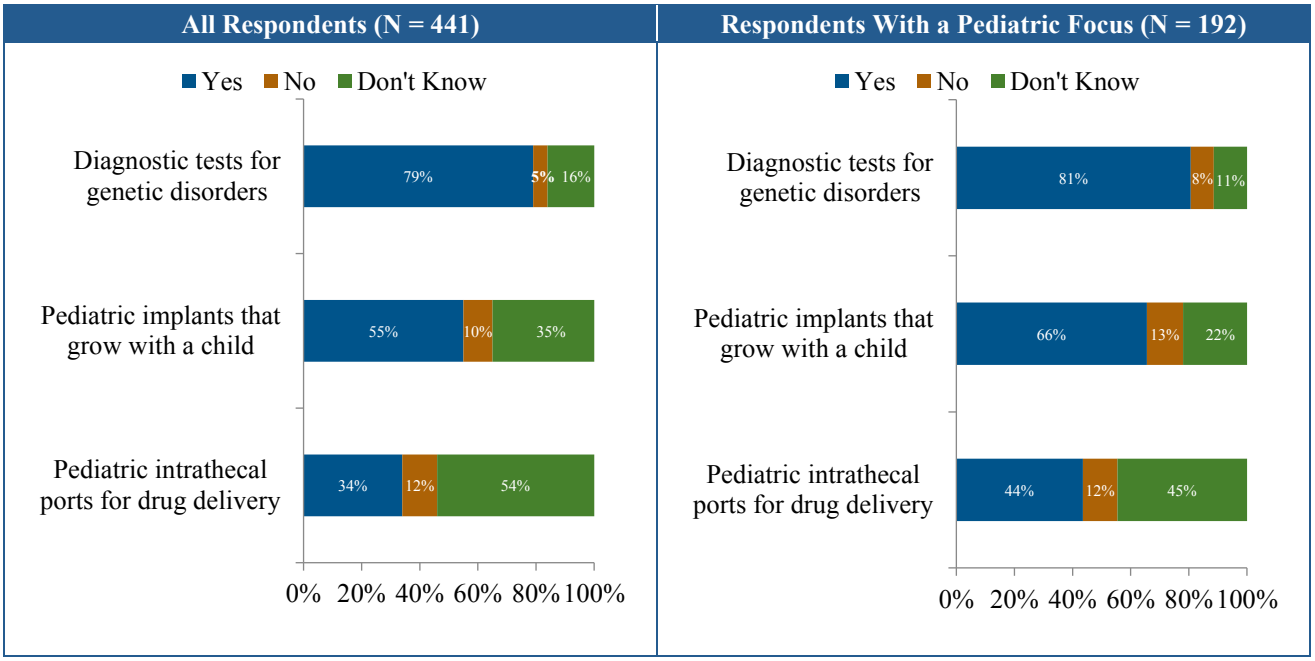
The survey aimed in part to assess the needs for those medical devices that may apply to more than one rare disease. A series of questions on this topic was asked of all respondents with either direct experience with rare disease populations or knowledge of rare diseases. Respondents were first asked 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%

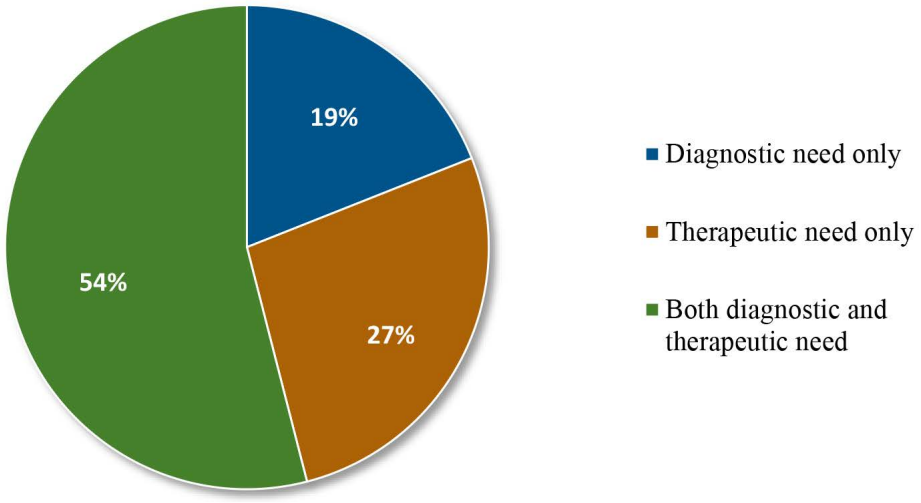
*Some needs were listed as both diagnostic and therapeutic; thus, the percentages for diagnostic and therapeutic needs may not equate to the percentage of all needs within a given medical category.

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).

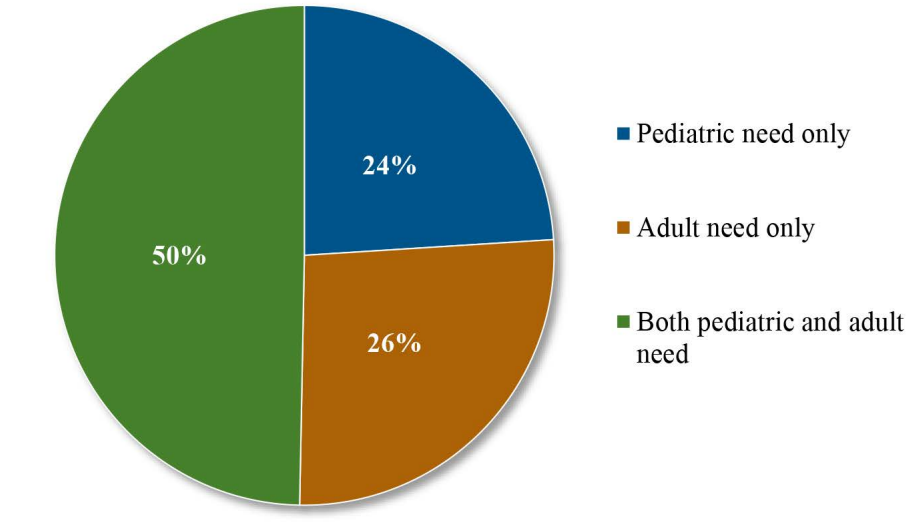
Figure 6: Need Type for Specified Rare Diseases*



*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

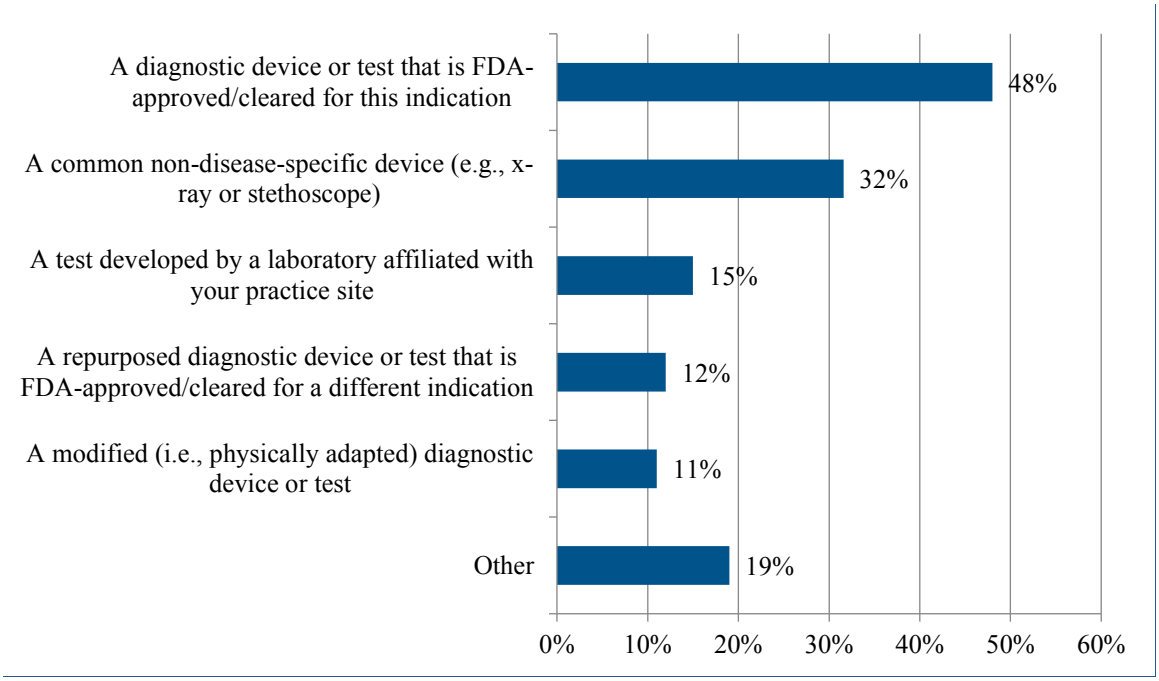
Diagnostic Device Needs in Various Settings

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.

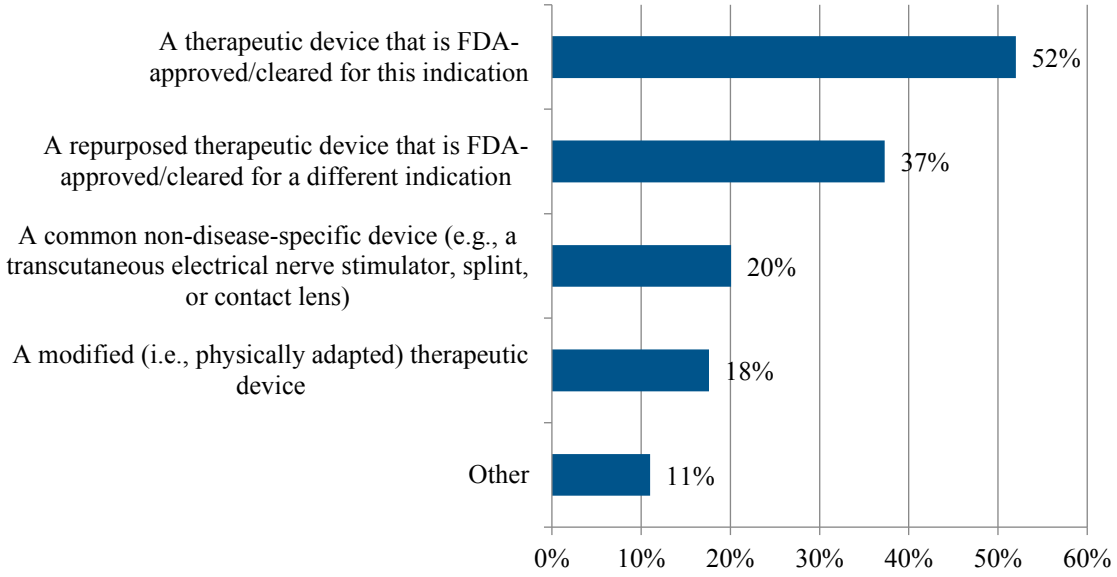
Uses and Limits of Current Therapeutic Devices

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.

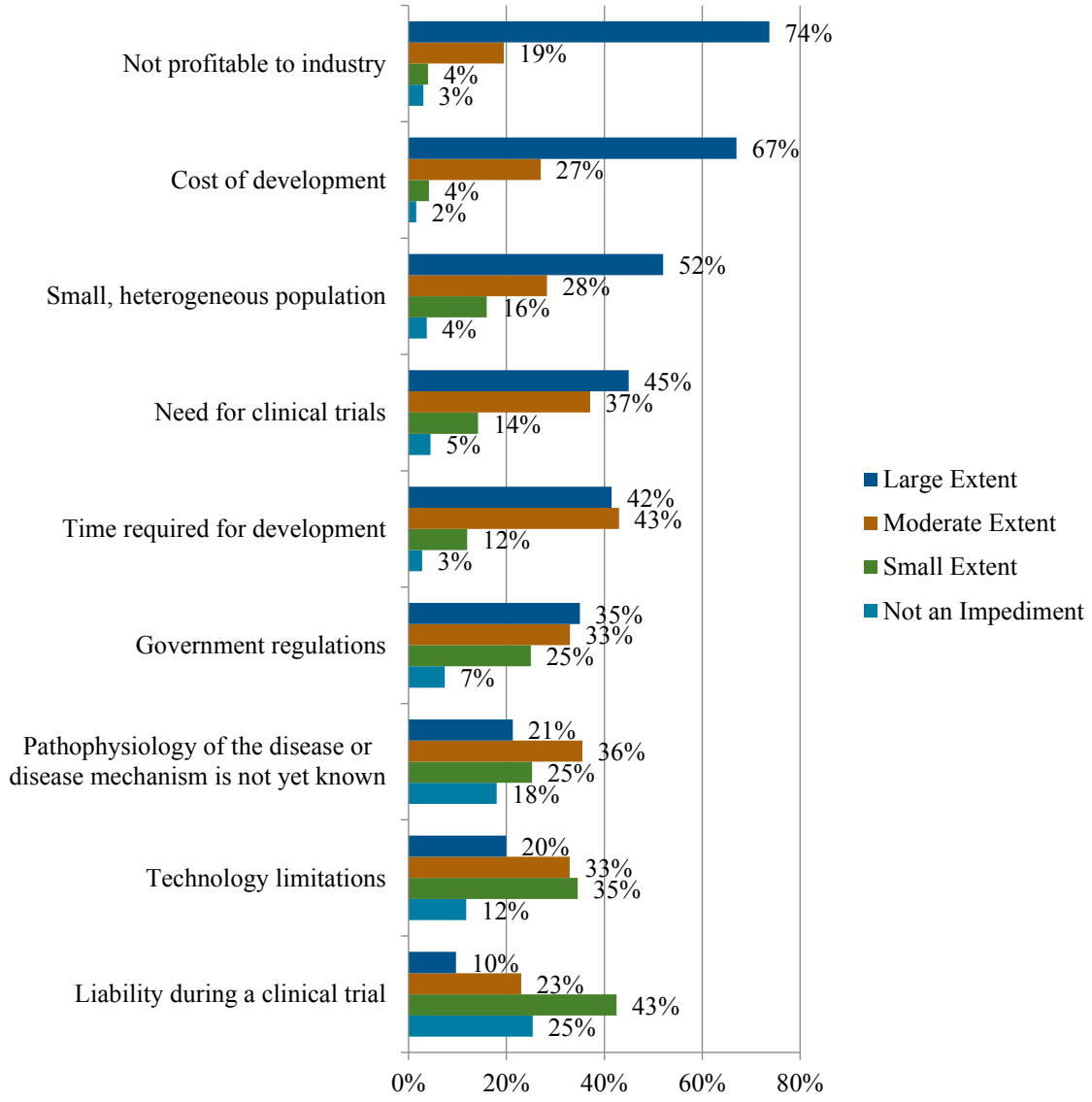
E. Meeting the Needs to Improve Diagnosis and Treatment

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.

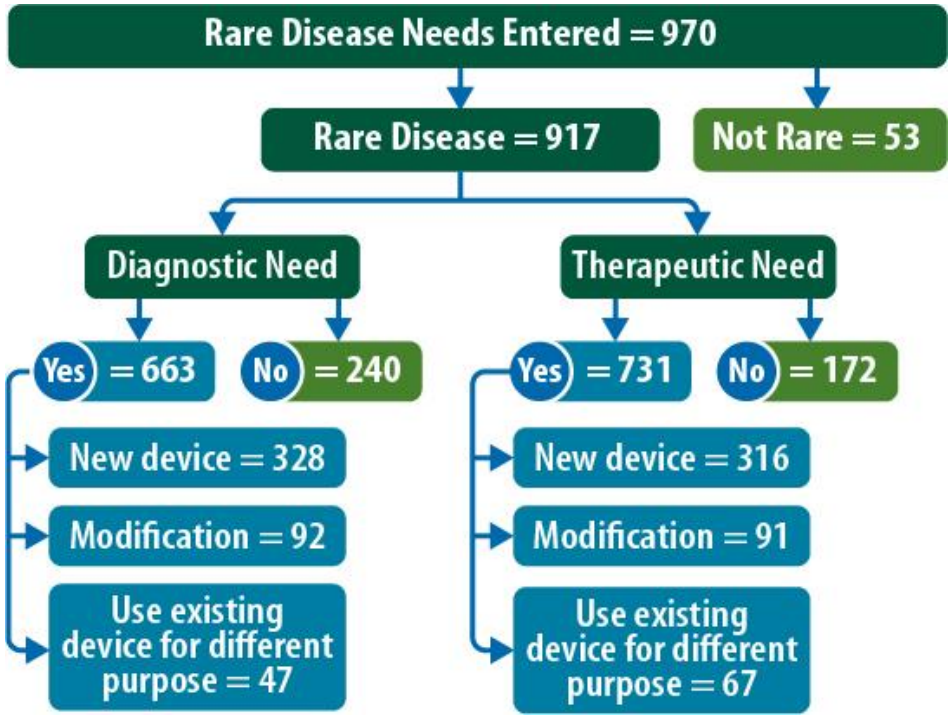
A total of 461 diseases/conditions covering all major medical specialties were suggested to have a diagnostic and/or therapeutic device need, with a majority of diseases/conditions mentioned only once, which highlights the quantity and heterogeneity of needs. It also emphasizes that needs exist across 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.