Challenges and Opportunities to Commercialize Orphan Drugs for Rare Diseases in the US

January 2019

Challenges and Opportunities to Commercialize Orphan Drugs for Rare Diseases in the US

George A. Chressanthis, Ph.D., Principal Scientist, Axtria Inc.
Animesh Arun, Senior Director, Axtria Inc.

> Investigating rare diseases gives researchers more clues about how the healthy immune system functions.
>
> ***Anthony S. Fauci, M.D.***
> *Director, National Institute of Allergy and Infectious Diseases*

> Cancer is really a slew of rare diseases. Lung cancer has 700 sub-types, breast cancer has 30,000 mutations which means that every cancer in its own right is a rare disease. Sharing data globally in this context is really important from a life-threatening perspective.
>
> ***Patrick Soon-Shiong, M.D.***
> *South African-born Chinese American surgeon, entrepreneur, and philanthropist*

1. Existence of Rare Diseases and White Paper Objectives

1.1 Existence of Rare Diseases

The global problem of addressing treatments for rare diseases (RDs) received significant awareness and encouragement of research & development (R&D) with the passage of the Orphan Drug Act of 1983 in the US, and similar legislation in the European Union (EU) (Regulation 141/2000 on Orphan Medicinal Products, 2000).[1] There is universal agreement about the success of the Orphan Drug Act in stimulating interest and bringing new drugs for the effective treatment of RDs. Multiple citations note there are about 7,000 RDs documented thus far, altogether affecting 25-30 million people in the US. The majority of RDs tend to be caused by genetic drivers and are present throughout life.[2-3] Thus a majority of RDs affect children.[2-3] Yet, despite a significant investment in the research, development, clinical trials, and approval of new drug therapies, effective treatments are available for only about 5% of RDs.[2-3] While variations exist in the definition of a "rare disease" around the world, there is a similarity in patient population and disease prevalence metrics from the US and EU: (US) disease or condition affecting fewer than 200,000 patients or 6.4 per 10,000 inhabitants, (EU) disease prevalence of 5 per 10,000 inhabitants or less.[3] The average global prevalence threshold is 4 patients per 10,000 people.[3]

1.2 Governmental Intervention and the Overarching Regulatory Environment for RDs

Because of the expectation of smaller addressable patient populations for RDs, governments may incentivize the development and commercialization of treatments for RDs and 'neglected diseases' – in which case they are together referred to as 'orphan diseases'. Relevant regulation includes the Orphan Drug Act of 1983 and the 21st Century Cures Act of 2016. Incentives to spur on the development and commercialization treatments for RDs can take multiple forms:

a) Market exclusivity over and above patent law.

b) Tax credits and carry-forward/carry-back provisions for orphan drug (OD) development costs.

c) Grants for drug development and funding for basic research.

d) Waiver of Prescription Drug User Fee Act (PDUFA) user fees.

e) Accelerated approval pathways (e.g., FDA Breakthrough Therapy designation).

f) Reduced statistical burdens for clinical development, given small population sizes (e.g., FDA Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD)).

1.3 White Paper Objectives

The preceding section illustrates a significant healthcare area for pharma companies, affecting a large number of patients with substantial unmet medical needs, though fragmented across a multitude of RDs. Pharma companies have focused greater R&D efforts over time on RDs given regulatory incentives. However, the model to launch and commercialize ODs is not the same as non-ODs. This white paper explores the unique challenges of ODs for RDs and the different approaches needed to address specific questions for their successful commercialization that vary from traditional launches of non-ODs.

2. Characteristics of Rare Diseases and Orphan Drugs

What are the characteristics of RDs and ODs that can affect the ability of a pharma company to commercialize new therapies in this area? A summary of characteristics and challenges exist from the IQVIA Institute for Human Data Science[2] that is supplemented by other studies cited on RDs (those citations are noted below for additional supporting evidence) and categorized into the following buckets:

- Genesis of RD Treatments and Categorization.
- Diagnosis Issues.
- Medical and Economic Burdens.
- Pricing and Value Assessment Issues.
- Role of Government at Rare Disease Patient Organizations (RDPOs).

Genesis of RD Treatments and Categorization

a) Many treatments for RDs are rooted in scientific advances (e.g., genetic testing, new therapy approaches, and use of biomarkers), faster product review times, and engagement by policy makers to increase the number of new treatments.[2]

b) Many treatments for RDs also take the form of innovative drug delivery mechanisms (targeted drug delivery) using existing active agents – e.g., using liposome-mediated delivery of antibiotic agents.

c) Relapsed and/or refractory diseases for many more-commonly occurring diseases that are considered treatable in their frontline population, are often considered RDs in their own right due to small patient populations, and the lack of effective treatment options at that point (e.g., relapsed/refractory acute lymphoblastic leukemia among the pediatric population).

Diagnosis Issues

d) RDs exist across a wide spectrum of disorders displaying numerous clinical signs and symptoms.[3] This also raises the possibility of errors in estimating true diagnosed prevalence, as noted by one research paper, "on rare diseases whose diagnosis rate may have changed over time, and raises the hypothesis that prevalence calculated from current incidence may be higher than diagnosed prevalence, which may lag behind the current disease definition and diagnostic methods."[3]

e) RDs are often difficult to diagnose with patients facing long evaluation times and multiple visits to physicians before a definitive answer is achieved.[2]

f) Patients face difficulties in finding physicians with the expertise to derive an accurate and speedy diagnosis.[2]

Medical and Economics Burdens

g) Many RDs cause chronic or progressive physical deterioration, disability, or early death with many starting in childhood.[3]

h) Significant burdens exist on patients, parents, and caregivers.[3] Patient journey analysis shows significant challenges and barriers for patients in the diagnosis, access, and treatment of RDs.[4-9]

i) Patient access in the US to payer subsidies for OD utilization varies by region, with the trend being for greater cost-shifting to patients, and thus increasing financial burdens.[2]

j) 2017 spending on OD indications in the US is about 9.6% of total drug spending on a base of $451 billion, with the trend showing moderate increases in the share of spending, possibly due to shifting financial burdens to patients to pay for ODs.[2]

k) The annual cost of an OD to a patient is inversely related to the number of patients being treated, with a high median annual cost of $46,800 in 2017 across all OD therapies, though reduced to $1,216 for the 10 RD therapies by volume of patients.[2]

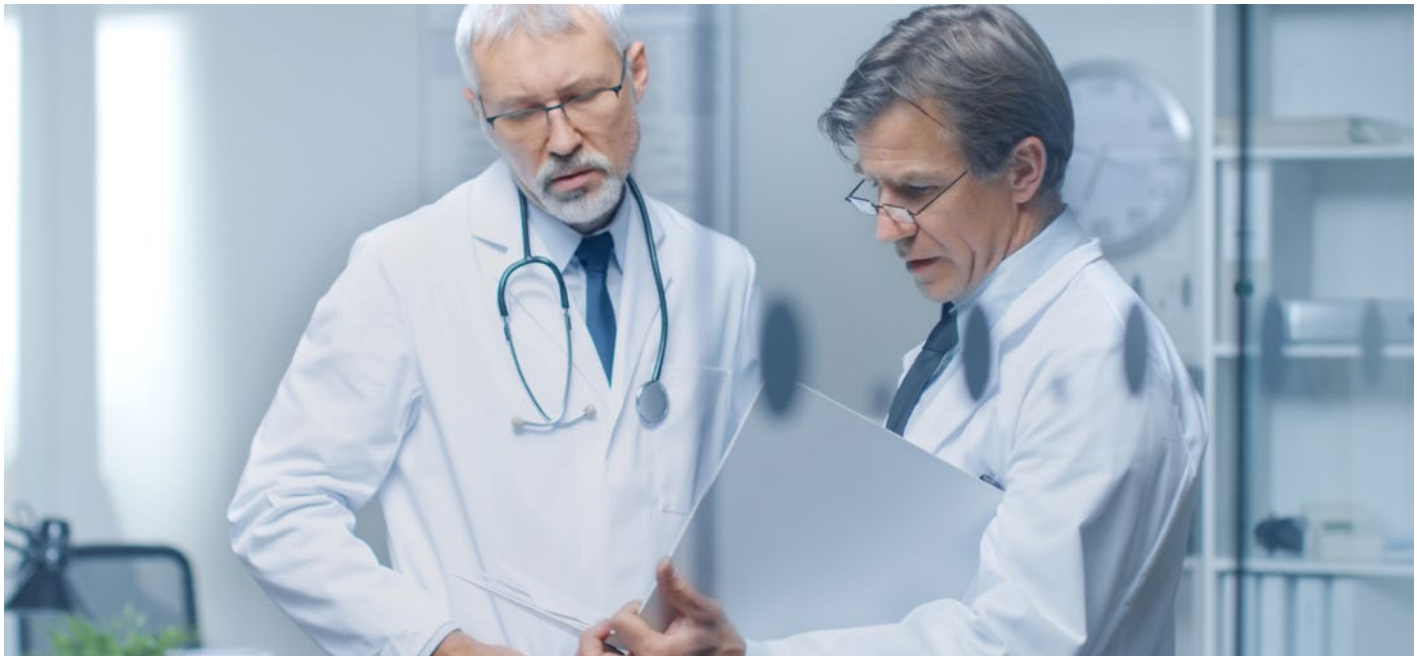
Pricing and Value Assessment Issues

l) Pharma companies may adopt indication-based pricing for drug treatments, reflecting both the drive to maximize revenues, as well as the need to apportion expenditures in development and additional clinical trials, over a smaller addressable patient population.

m) Unique to RDs are challenges involving research and health technology assessment, clinical outcome assessment, valuation of drugs for RDs, and the use of traditional health economic models of outcome assessment that may not apply or require adjustments when applied to ODs.[10-14]

Role of Government and RDPOs

n) Globally, significant variations exist in governmental reimbursement for ODs with questions being raised on the societal tradeoff on spending significant resources for RDs affecting few people.[15-18]



o) 503 ODs as of August 2018 have been approved since the passage of the Orphan Drug Act, with 78% having orphan-only indications while 22% having both orphan and non-orphan indications.[2] The growth of non-orphan indications from OD applications is the likely reason for the reduction in the tax credit for OD clinical trial costs from 50% to 25%.[2]

p) Rare disease patient organizations (RDPOs), defined as non-profit organizations representing the needs of patients with RDs, play an increasingly important role in advocating research for RDs, prioritizing RD research by governments and pharmaceutical companies, and promoting greater involvement of patients and related individuals in research.[19]

The preceding points suggest a very different commercialization model of ODs for RDs than the one used for non-ODs for non-RDs. The next section will note key strategic and tactical plans necessary for the successful commercialization of ODs for RDs.

3. Commercialization Elements for Orphan Drugs

The successful commercialization of ODs requires a range of strategic and tactical elements to implement from pharma companies. The elements are listed in approximate chronological order according to the life-cycle of the project/product, from the clinical trial stage through to post-launch:

- Development of Patients for RD Clinical Trials.
- Improvement in RD Diagnosis and Treatment.
- Market Access and Patient Affordability.
- Pre-Launch Preparations.
- Sales and Marketing Activities.
- Specialized Supply Chain Development.
- Engagement with Governmental Agencies and Policy Decisionmakers.
- Greater Within Pharma Company Cross-Functional Collaboration.

Development of Patients for RD Clinical Trials

a) **Pharma companies need to work closely with patients and RDPOs for the recruitment of patients for clinical trials.** While finding appropriate patients is always a challenge for the conduct of clinical trials, this is especially acute for RDs given the small populations involved. This means pharma companies must develop strong relationships with all key RDPOs and research hospitals (e.g., children's hospitals, key academic research hospitals, etc.) for the recruitment of patients. This places even greater weight on external medical affairs teams to foster these key relationships with Key Opinion Leaders (KOLs) and RD experts.

Improvements in RD Diagnosis and Treatment

b) **Pharma companies need to collaborate and share data on RD mechanism discovery.**[20] Unfortunately, many RDs facing patients go unsolved. This means pharma companies working closely with major research centers working on RDs, governmental agencies and RDPOs, and collaboration with other companies and organizations on data sharing. There also needs to be an international network for data and information sharing for undiagnosed patients. A publicly-funded initiative, the NHS Genomic Medicine Service aims to make available genomic data, as well as anonymized health records of patients accessible for research around rare disease pathways, diagnosis and prediction of incidence, and development of personalized treatments and interventions.[21-22] Some pharma companies are also investing in genomic research for RD mechanism discovery and development of personalized targeted and immunotherapies.[23]

c) **Create a faster pathway for patient access to an accurate diagnosis.**[20] As noted in the previous section, patients with RDs spend a long time getting their disease properly diagnosed. In certain disease states, it is common for patients to cycle between physicians for months or years, before the disease is diagnosed. This means pharma companies must make it easier for patients to access information, make it more affordable for patients to conduct necessary tests to determine their RD, and work with payers on the cost-effectiveness of providing healthcare subsidies to support faster detection of RDs. In addition, there is likely an application of Artificial Intelligence (AI) and Machine Learning (ML) techniques to data around current diagnosed RD patients, in determining the attributes associated with an accurate RD diagnosis in order to shorten this pathway. This can help define metrics that physicians and patients can use to diagnose RDs accurately and quickly.

d) **Education of physicians and engagement of patients.**[20] The preceding points illustrate the need for pharma companies to develop a more patient-centric model than the current approach which is more physician-centric. Patients diagnosed with RDs are highly motivated, engaged, and informed. This means a strong digital and social media presence to engage both physicians and patients. There may be a role for patient support infrastructure, such as Patient Hubs, to help pull-through patients by providing patient support for gaining access to therapy, and continued engagement with patients and physicians to help drive adherence to prescribed therapy.

e) **Creation of a RD physician registry for patients.** Pharma companies need to develop an extensive database of physicians by RD and share such information with patients. One reason for patients having longer diagnosis times for their RD is not being able to find a physician expert who can accurately diagnose and treat their RD. Expertise in RD diagnosis and treatment tends to be concentrated among a small subset of specialists, and often in academic hospitals.

Market Access and Patient Affordability

f) **Pharma companies need to develop strong health economic models for RDs to demonstrate the value to payers (private health insurance and government) to subsidize patient healthcare costs.**[20] This means even a closer connection of health economic and outcomes research (HEOR) and real world evidence (RWE) analyses with commercial modeling than what is currently conducted. Prior research cited noted that RDs often result in chronic and debilitating conditions that are costly for patients to treat. Drug costs are also an issue given the small volume of patients. Drug price elasticity analysis combined with HEOR/RWE will be necessary to determine the economic burden to patients but also to payer plans and healthcare systems if these RDs go untreated. This means performance-based contracts for ODs are much more likely than for non-ODs. Thus, the ability to link and track HEOR/RWE analysis with these payer contracts will be critical. The use of AI/ML technology to produce ongoing updates on projected health and economic outcomes will also be more critical than for non-ODs.

g) **Pharma companies need to develop a payer registry on health plan coverage of RDs.** Healthcare coverage of RDs significantly varies by plan and region. Patients absorb a significant cost-burden in the treatment (drug and overall healthcare costs) of RDs. Such a registry needs to be shared with patients so they can plan accordingly on the cost-outlays required to obtain treatment of their RD. A payer registry can also be of benefit to a pharma company in planning their payer strategy and tactics necessary to support RD patients (e.g., the distribution and amount of copay support and discounts/rebates to payers/pharmacy benefit managers (PBMs)).

h) **Strong database management and linkages used to complete HEOR/RWE and traditional commercial analytics will be required for accurate RD analyses and insight.** The small number of patients with RDs will mean that the ability to link databases without losing data is paramount. Losing data with non-ODs may not have significant ramifications, but this is very different for ODs. This database capability will affect a wide range of clinical, on-going HEOR/RWE analyses for payer contracts, and sales and marketing activities.

i) **Mechanisms must be in place to allow for continued real-time monitoring by pharma companies of patient medical progress with RDs taking ODs.** Wearable and implant devices have already been increasing in their utilization by pharma companies and patients to monitor patient progress with various conditions. Such devices will be even more critical given the cost of ODs for payers to subsidize coverage and/or for pharma companies to provide real-time patient information to support performance-based payer contracts.

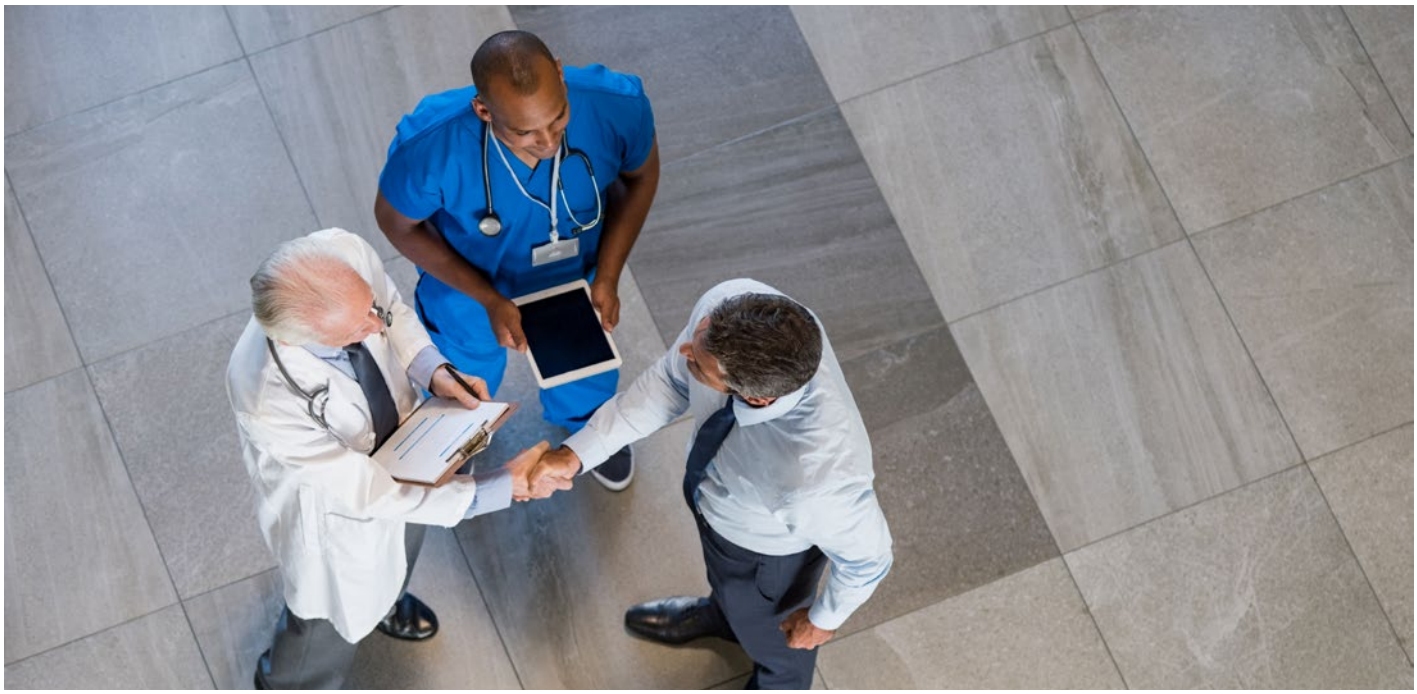
Pre-Launch Preparations

j) **Stronger efforts are needed by pharma companies pre-launch to ensure a successful OD launch.** The small number of patients for each OD to treat a RD means the margin of error from a financial standpoint is substantial for not having an accurate forecast of projected diagnosed patients. An inaccuracy of just a small number of patients can have significant financial implications. Thus, not building an accurate patient-base can have significant consequences on the cost/OD (as drug cost is strongly inversely related to patient volume). Further, epidemiology-driven forecasts must estimate testing rates, diagnosis rates, as well as trends and leverage points to drive testing and diagnosis rates. Further, there may be an initial one-time 'bolus' of untreated patients who had exhausted other treatment alternatives. This places greater importance on the validity and data used in prevalence and patient flow models to develop accurate patient forecasts.

Sales and Marketing Activities

k) **Strong digital and social media presence will be required for pharma companies to engage patients, caregivers, physicians, and KOLs.** As noted before, RD patients and their caregivers are a highly motivated and engaged population. Pharma companies must provide access to useful and timely information to patients, caregivers, physicians, and KOLs to continue their engagement and trust in their actions.

l) **Greater support for caregivers and their needs.** Pharma companies need to go beyond the drug when it comes to providing patient support. For example, the majority of RDs affect children, thus the role and needs of caregivers are paramount. Social and economic support programs for caregivers will be necessary for the continued engagement and treatment of RD patients. In some cases, diseases may be progressive and eventually terminal, and treatments may be palliative. Great sensitivity to patients and caregivers must be applied into the design of patient materials and their touchpoints with patient support infrastructure, such as Patient Hubs and Clinical Educators.



m) **Engaging in "patient-journey" analysis will be critical for pharma companies to understand RD patient needs.** The patient-journey for those with RDs can be long and arduous. Pharma companies need to understand this journey, identify the crucial leverage points, and be able to intervene to help prevent or ease roadblocks that can impede diagnosis and treatment. This also means the patient-journey must be geographically incorporated into the go-to-market model, target selection, territory alignment design of sales representatives, including accounting for the layout of healthcare systems and payer health plans. Further, the role of healthcare providers in the patient journey is crucial to an understanding of their role in the disease-state and should drive segmentation and the tonality of messaging directed at healthcare providers.

n) **Sales and marketing strategy and tactics must be strongly "informative" in intent as opposed to the current "persuasive" approach used by pharma companies.** Pharma companies must stress value-based messaging using scientific/clinical/medical information and evidence given the complexity of the RDs being treated by ODs, the sophistication and expertise of physician specialists, and the well-informed nature of patients and caregivers. This means a strong linkage to personnel in medical affairs who can deliver more peer-to-peer engagements with physician specialists will be essential. This also means RD sales forces will likely be very small given small patient populations, with each representative covering a large geography targeting physician specialists in major metropolitan areas. Sales reps must also be highly specialized and capable to deliver complex scientific/clinical/medical messages. Their backgrounds must be Medical Science Liaison (MSL)-like in their ability to engage physician specialists at an advanced level.

Specialized Supply Chain Development

o) **Understanding the distribution of ODs for RDs through specialty pharmacy and buy-and-bill channels is important.** The delivery of ODs to patients with RDs will likely take a different pathway than drugs for traditional non-OD conditions. This means capturing ODs going through specialty pharmacy channels and administered in non-office-based retail channel settings (e.g., hospitals, clinics).

p) **Specialized supply chains may be needed for certain OD treatments.** In some cases, notably gene-and-cell based-immunotherapies, a two-way supply chain with specialized 'treatment sites' is needed to collect cells from patients, manufacture the immunotherapy, and ship the manufactured cells back to a specialist site that can administer the therapy and manage any patient complications.

Engagement with Governmental Agencies and Policy Decisionmakers

q) **Pharma companies must actively engage with governmental agencies and policy decisionmakers to address the economic and social impact of RDs.** RDs affect 25-30 million people in the US with the majority of those RDs affecting children as previously noted. It is therefore essential that pharma

companies have a continued presence at public policy forums to highlight the economic and social burdens of people and society due to RDs. Further, pharma companies should promote policy actions that can be taken by the government to encourage continued development of new therapies and ease the burden of patients, caregivers, and the healthcare system due to RDs. Lastly, given the context of improvements in overall public health, there are constrained resources available for healthcare. Spending on RDs needs to be considered in this overall context of affordability and what you get for each healthcare dollar.

Greater Within Pharma Company Cross-Functional Collaboration

r) **Greater cross-functional collaboration with internal pharma organizational units must exist for successful commercialization.** Finally, the preceding commercialization elements illustrate the need for greater cross-functional collaborations from scientific, clinical, pre-launch, launch, and post-launch phases of the product/drug life-cycle than what is typically seen in a pharma company.

4. Conclusions

ODs for RDs present pharma companies with the opportunity to address a substantial unmet medical need, with approximately 7,000 RDs, and only about 5% having effective treatments. A large number of patients in the US are affected with these RDs (around 25-30 million people). The majority of RDs affect children. Also, RDs often translate into chronic and deteriorating conditions for patients, the majority being affected and starting in childhood, and often resulting early death. Significant economic and social burdens exist for patients, caregivers, and the healthcare system to treat RDs. Lastly, what is clear from the preceding review and analysis is that the commercialization of ODs for RDs is very different from non-ODs for non-RDs, requiring a pharma company to think and act differently. In many ways, the commercialization of ODs for RDs represents a special case of the industry's shift to specialty medicines and how pharma companies must differently respond to these new challenges.

References

1. Auvin S, Irwin J, Abi-Aad P, et al. The problem of rarity: estimation of prevalence in rare disease. *Value in Health* 2018; 21: 501-507.
2. IQVIA Institute for Human Data Science. Orphan drugs in the United States: growth trends in rare disease treatments. IQVIA Institute for Human Data Science, published online 17 October 2018, available at https://www.iqvia.com/institute/reports/orphan-drugs-in-the-united-states-growth-trends-in-rare-disease-treatments.
3. Copley-Merriman K. Rare diseases: addressing the challenges in diagnosis, drug approval, and patient access. *Value in Health* 2018; 21: 491-492.
4. Bruni S, Lavery C and Broomfield A. The diagnostic journey of patient with mucopolysaccaridosis I: a real-world survey of patient and physician experiences. *Molecular Genetics and Metabolism Reports* 2016, 8: 67-73.
5. Garau R. The medical experience of a patient with a rare disease and her family. *Orphanet Journal of Rare Diseases* 2016; 11: 19. DOI 10.1186/s13023-016-0401-7.
6. Zurynski Y, Deverell M, Dalkeith T, et al. Australian children living with rare diseases: experiences of diagnosis and perceived consequences of diagnostic delays. *Orphanet Journal of Rare Diseases* 2017; 12: 68. DOI 10.1186/s13023-017-0622-4.
7. Ferrara L, Morando V and Tozzi V. The transition of patients with rare diseases between providers: the patient journey from the patient perspective. *International Journal of Integrated Care* 2017; 17: A157. DOI: http://doi.org/10.5334/ijic.3465.
8. Mehta A, Belmatoug N, Bembi B, et al. Exploring the patient journey to diagnosis of Gaucher disease from the perspective of 212 patients with Gaucher disease and 16 Gaucher expert physicians. *Molecular Genetics and Metabolism* 2017; 122: 122-129.
9. De Vries E, Fransen L, van der Aker M, et al. Preventing gatekeeping delays in the diagnosis of rare diseases. *British Journal of General Practice* 2018; 68: 145-146.
10. Nestler-Parr S, Korchagina D, Toumi M, et al. Challenges in research and health technology assessment of rare disease technologies: report of the ISPOR rare disease special interest group. *Value in Health* 2018; 21: 493-500.
11. Phillips D and Leiro B. Clinical outcome assessments: use of normative data in a pediatric rare disease. *Value in Health* 2018; 21: 508-514.
12. Ollendorf D, Chapman R and Pearson S. Evaluating and valuing drugs for rare conditions: no easy answers. *Value in Health* 2018; 21: 547-552.
13. Pearson I, Rothwell B, Olave A, et al. Economic modeling considerations for rare diseases. *Value in Health* 2018; 21: 515-524.
14. Benjamin K, Vernon M, Patrick D, et al. Patient-reported outcome and observer-reported outcome assessment in rare disease clinical trials: an ISPOR COA emerging good practices task force report. *Value in Health* 2017; 20: 838-855.
15. Schlander M, Dintsios C-M and Gandjour A. Budgetary impact and cost drivers of drugs for rare and ultrarare diseases. *Value in Health* 2018; 21: 525-531.
16. Bourke S, Plumpton C and Hughes D. Societal preferences for funding orphan drugs in the United Kingdom: an application of person trade-off and discrete choice experiment methods. *Value in Health* 2018; 21: 538-546.
17. Magalhaes M. Can severity outweigh smaller numbers? A deliberative perspective from Canada. *Value in Health* 2018; 21: 532-537.
18. Dharssi S, Wong-Rieger D, Harold M, et al. Review of 11 national policies for rare diseases in the context of key patient needs. *Orphanet Journal of Rare Diseases* 2017; 12: 63. DOI 10.1186/s13023-017-0618-0.
19. Pinto D, Martin D and Chenhall R. The involvement of patient organizations in rare disease research: a mixed methods study in Australia. *Orphanet Journal of Rare Diseases* 2016; 11: 2. DOI 10.1186/s13023-016-0382-6.
20. Austin C, Cutillo C, Lau L, et al. Future of rare diseases research 2017-2027: an IRDiRC perspective. *Clinical and Translational Science* 2018; 11: 21-27.
21. *The Economist*. The NHS genomic service could transform medicine. Published online 27 September 2018, available at https://www.economist.com/britain/2018/09/27/the-nhs-genomic-service-could-transform-medicine.
22. NHS England. NHS genomic medicine service. Published online and available at https://www.england.nhs.uk/genomics/nhs-genomic-med-service/.
23. Regeneron®. Regeneron® genetics center. Published online and available at https://www.regeneron.com/genetics-center.

George A. Chressanthis, Ph.D.
Principal Scientist, Axtria Inc.
300 Connell Drive, Suite 5000
Berkeley Heights, NJ 07922
E: george.chressanthis@axtria.com

Animesh Arun
Senior Director, Axtria Inc.
300 Connell Drive, Suite 5000
Berkeley Heights, NJ 07922
E: animesh.arun@axtria.com

Contact Us

+1-877-9AXTRIA
info@axtria.com

Disclaimer

Axtria® understands the compliance requirements behind personalization and we do not work with any personally identifiable data that can identify an end-customer of a business.

We have the strictest data security guidelines in place as we work with businesses to improve the experience for their customers.

www.axtria.com
facebook.com/AxtriaInc/
info@axtria.com
linkedin.com/company/axtria
@Axtria

Founded in 2010, Axtria® is a Big Data Analytics company which combines industry knowledge, analytics and technology to help clients make better data-driven decisions. Our data analytics and software platforms support sales, marketing, and risk management operations in the life sciences, finance, retail, and technology industries. We serve clients with a high-touch on-site and onshore presence, leveraged by a global delivery platform that focuses on reducing the total cost of ownership with efficient execution, innovation, and virtualization.

For more information, visit www.axtria.com

Follow Axtria on Twitter, Facebook and LinkedIn