Clinical Trials Intelligence

Biomarker Roles within Clinical Trials

An Analysis of Clinical Trials from 2007-2011 and 2012-2016.
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April 2017

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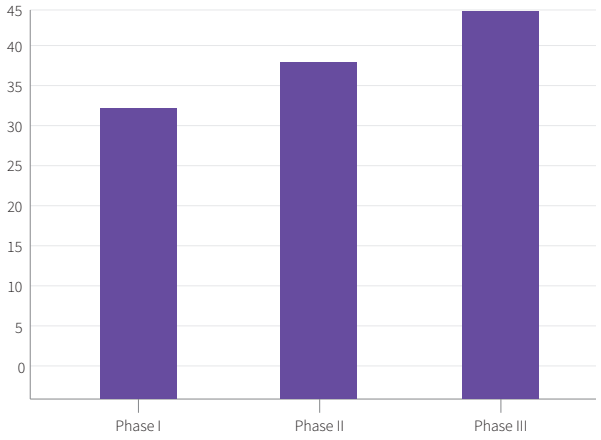
There is a lot of discussion across biopharma about the increasing complexity in the design and management of clinical trials. Recent estimates suggest the cost of bringing a drug to market is as high as $3 billion, and only one in 10 drugs successfully navigate the process and make it to market. These trends are not sustainable, and the use of targeted clinical strategies is being seen as a critical step towards improving success rates.

In this paper we examine the application of specific biomarker roles (therapeutic effect marker, toxic effect marker, disease marker). In this regard we analyzed the growth in the application of different biomarker roles across multiple indications with some interesting trends that will be relevant to clinical development professionals. While we note the overall increase in the use of biomarkers, that growth is not uniform across all biomarkers with important implications given the continued high level of unproven efficacy across late-stage trials.

The increase in complexity has triggered a considerable extension in the average duration of clinical trials and a reduction in the differential duration of trial phases.[1] (See Figure 1.)

Any increase in trial duration leads to increasing costs, delays to launch and the potential for a drug to miss the vital slot as first-in-market, holding back potentially lifesaving treatments for patients. Development strategies need to ensure that the launched compound can demonstrate sufficient efficacy while avoiding excessive recruitment demands, undesired toxicity and costly trial amendments.

Figure 1: Mean Phase Length in Months



While timelines are extending sharply, notably in oncology, we also note a significant rise in the volume of trials. Analyzing the number of trials within *Cortellis Clinical Trials Intelligence* with a "Start Date" each year between 2007 and 2016 we see an ongoing rise in the number of trials. During our two comparison periods, January 1, 2007 - December 31, 2011 (2007-2011) against January 1, 2012 - December 31, 2016 (2012-2016), we see a 33% increase in the number of trials.[2] (See Figure 2.)

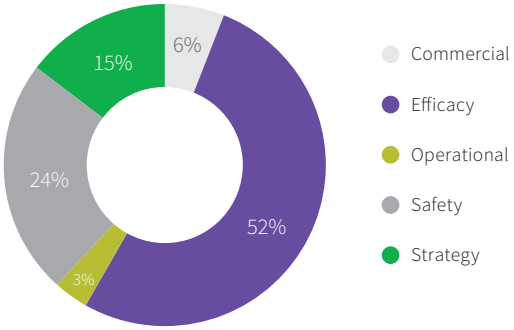
Figure 2: Trials Commenced by Year 2007-2016

Source: [1] *Journal of Health Economics, DiMasi, Joseph A, Grabowski Henry G & Hansen, Ronald W. "Innovation in the Pharmaceutical Industry: New Estimates of R&D Cost." 47, 20-33 (2016).*
[2] *Cortellis Clinical Trials Intelligence, Clarivate Analytics, March 15, 2017.c*

We believe the increasing volume of trials has implications for patient recruitment and competition, but also specifically relevant to this analysis, a heightened need to ensure that the clinical strategy is based on the best available intelligence relating to disease mechanisms, target actions and patient segmentation.

To understand whether the fundamentals of the underlying biological models are keeping pace with the complexity of trials, we consulted a recent published analysis. This demonstrated that the overwhelming majority of reasons given for failure are not due to strategic reasons, but are due to unproven efficacy (52%) and safety issues (24%) highlighting the importance of a solid biological rationale, suggesting scientific inadequacies in the understanding of the underlying disease mechanism, understanding of the drug action and the selection of patient cohorts.[3] (See Figure 3.)

Figure 3: Trial Failures



Patient populations are diverse and a treatment that is effective and safe in one sub-population may not be similarly beneficial and may introduce additional toxicity in other groups. Patient segmentation utilizes molecular sub-types for the design of trials with the aim of increasing the likelihood of proving the efficacy of the targeted therapies under development, while reducing or eliminating the impact of known actions that may increase the frequency of non-responders or serious adverse events. The effective applications of biomarkers are critical in the definition of a patient segmentation strategy and trial inclusion criteria. A patient segment that is too broad may lead to unproven efficacy; conversely a model based on incorrect assumptions may have implications for both efficacy and safety and an extremely tight patient segment may lead to challenges in patient recruitment.

New drugs employing such a targeted approach have transformed our ability to treat specific diseases, but also highlighted the potential for therapeutic development and patient care when a strong biomarker strategy is employed. Within Chronic Myeloid Leukemia (CML) and Acute Myeloid Leukemia (AML) patients who are Philadelphia Chromosome-positive, Imatinib has validated the clinical strategy by providing a significantly improved five-year survival rate for CML patients of 81%, up from 31%.[4]

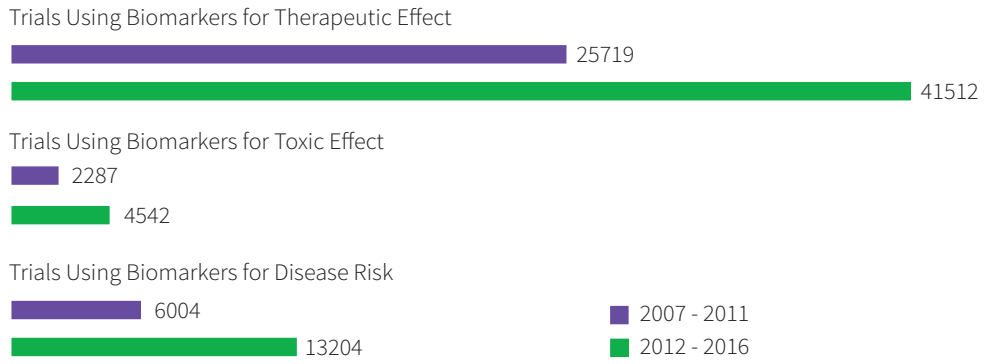
This improvement in patient care is also reflected in other examples where the confidence and validity of the clinical strategy has been used to define a specific patient population, reduce risk and ultimately shorten time to market, particularly when it enables the granting of a Facilitated Regulatory Pathway. Historically, drug approvals sought to maximize the potential market opportunity both in the initial indication and later line extensions. The rising average duration of trials suggests that a change in strategic approach is valuable, particularly after the recent successes with drugs like Imatinib and Keytruda. Keytruda developed by Merck is indicated for patients with metastatic or advanced non-small cell lung cancer who test positive for TPS>1% PD-L1 expression and negative for EGFR and ALK mutations. This new drug has a mechanism of action that is so tightly understood and critically linked to a clear biomarker strategy that development professionals had the confidence to carefully select patients from specific sub-groups from the earliest trials and demonstrate efficacy from the earliest opportunity, leading to a uniquely accelerated approval and ultimately benefiting both patients and Merck with the granting of a Marketing Authorization.

To determine whether these celebrated successes reflect the beginning of a new stage of therapeutic evolution, we wish to understand how deep the shift has occurred towards personalized therapies and how widespread such an approach is across the therapeutic areas within clinical development. By comparing the two periods, 2007-2011 vs. 2012-2016, we can identify a number of trends in the application of biomarkers within active clinical trials that demonstrate an increase in both the application of specific biomarker types and roles, also highlighting some areas where there are opportunities to increase our knowledge of the underlying biological mechanisms.

Source: [3] *Nature Reviews Drug Discovery, Harrison RK. "Phase II and Phase III Failures 2013-2015." 15, 817–818 (2016)*

We analyzed a total database of 263,210 clinical trial records within *Cortellis Clinical Trials Intelligence*, each record representing a single clinical trial, populated from intelligence gathered from 30 global trial registries and additional published source references. (See Figure 4.)

Figure 4: Number of Trials Using Specific Biomarker Roles, 2007-2011 - 2012-2016

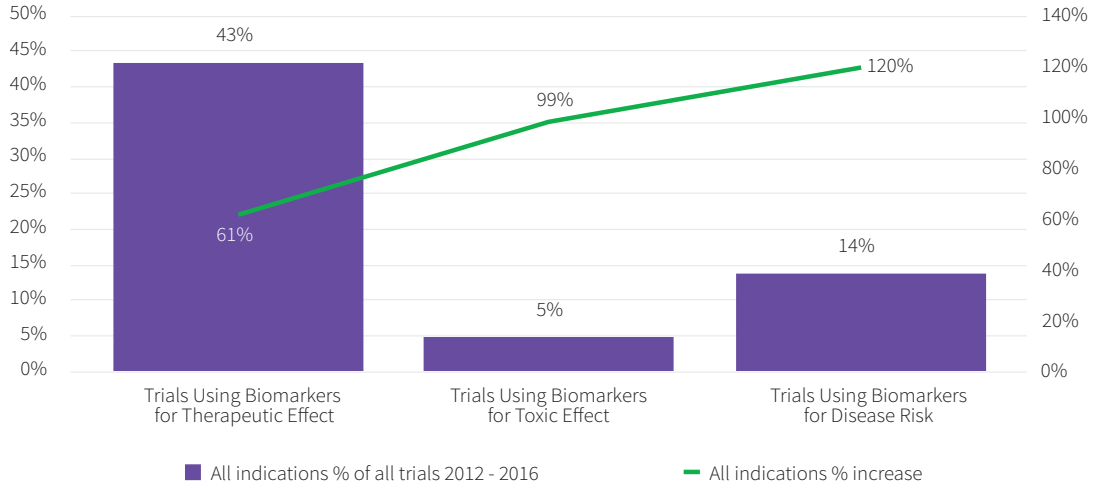


As expected, our analysis confirmed that the use of biomarkers is increasing. Examining trials from 2007 to 2016, we see a rise in the number of trials commenced. From 2007-2011, there were 71,735 while from 2012-2016 we found 95,552. This is an increase of 33%, with a significantly higher corresponding jump in the application of biomarkers to assess therapeutic effect, toxicity and disease. When analyzing the role of all biomarkers we see that markers of disease increased by 120% over the time period, followed by markers for toxic effect, 99%, and therapeutic effect markers at 61%.

To focus on our analysis of growth in the application of specific biomarker types, we examined the relationship between growth in the utilization of specific biomarker roles against the current level of use of each role. (See Figure 5.)

Here we can see that while therapeutic effect markers are the most commonly employed in 43% of trials, at a 61% growth rate, they are not growing in utilization as fast as toxic effect, 99%, or disease at 120%. Given the relatively low historical application of toxic effect and disease markers, this investment in clinical programs will shape future therapies available to patients.

Figure 5: % of Total Trials Using Specific Biomarker Roles Against Growth in the Application of Biomarker Usage



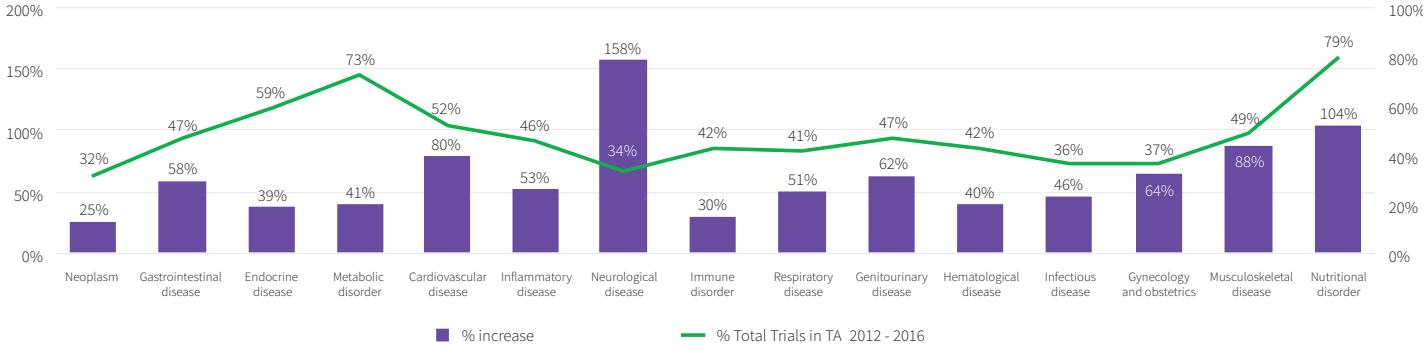
Source: *Cortellis Clinical Trials Intelligence, Clarivate Analytics, March 2017.c.* [4] *New England Journal of Medicine, Druker BJ, et al. "Five-Year Follow-up of Patients Receiving Imatinib for Chronic Myeloid Leukemia." 355, 2408-2417 (2006)*

Given the overall strength of growth across all biomarker roles across all indications, an examination of individual therapeutic groups will highlight those areas experiencing the highest level of growth and currently undergoing the most dramatic transformation. We will examine therapeutic effect markers, toxic effect markers and disease markers within therapy areas (TAs) that demonstrated the highest levels of transformation.

Looking at the growth in application of therapeutic effect markers, nutritional disorders display a rapid growth rate against a high base level. Neurological disease is clearly experiencing a period of rapid growth in the application of therapeutic effect markers against a lower relative base, along with cardiovascular disease and musculoskeletal disease. We can also observe the appearance of gynecology and obstetrics as high growth areas for therapeutic effect markers as being notable for not appearing as highly in any of the other categories. (See Figure 6.)

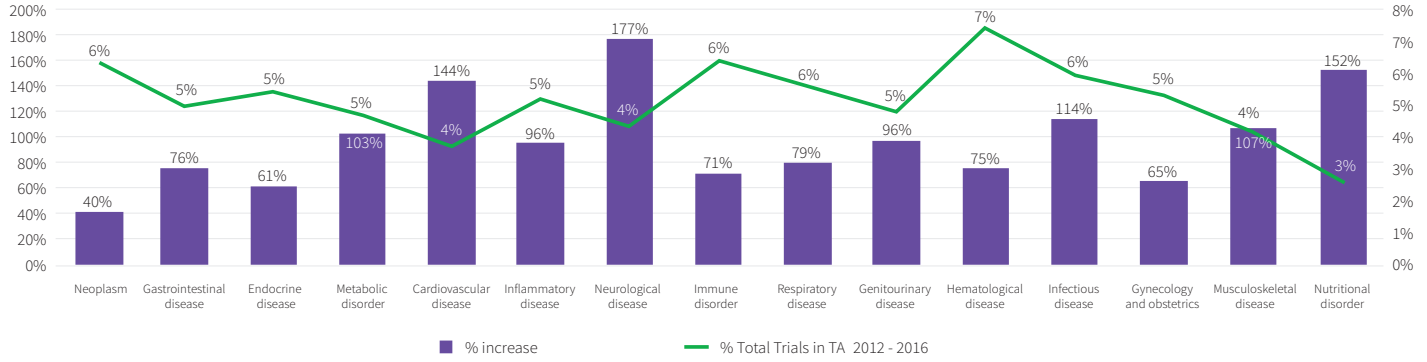
"We will examine therapeutic effect markers, toxic effect markers and disease markers within therapy areas that demonstrated highest levels of transformation.

Figure 6: Growth in the Application of Therapeutic Effect Biomarkers Against Current % Share of Trials Within the Same Therapy Area (TA)



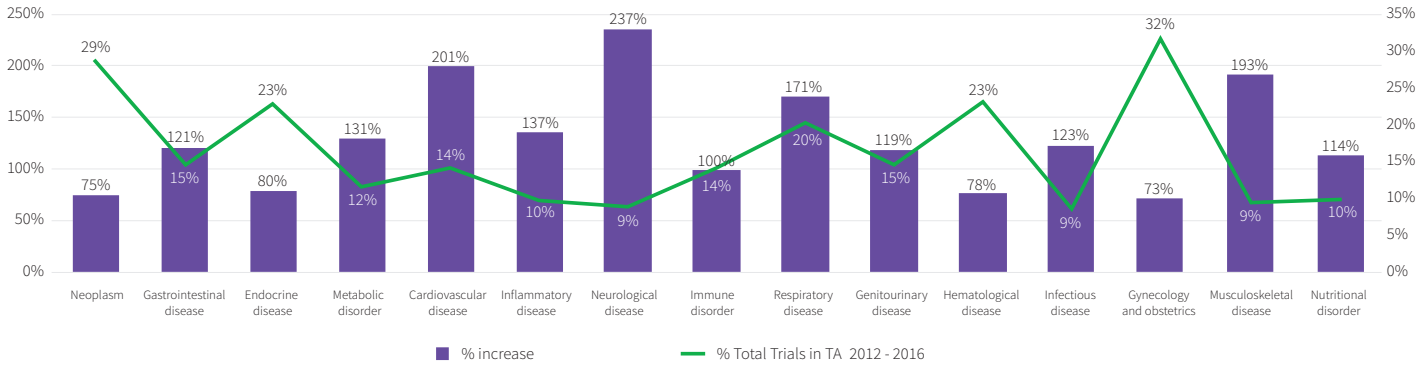
While the overall adoption of toxic effect markers is lower than other roles, there is strong evidence of growth in both established and emerging therapeutic areas. Despite the relatively strong presence of oncology in this list in respect of total volumes as a percentage of all TA trials, oncology does not appear on our list of highest growth areas for application of toxic effect markers. Similarly, metabolic disorders have a high rate of current utilization, but a lower level of increase. The highest growth therapy areas within the high volume groups are neurological disease at 177%, cardiovascular disease at 144% and infectious diseases at 114%. Within the lower volume groups, nutritional is again an area of clear growth at 152%, along with musculoskeletal disease at 107% and metabolic disorder: 103%. (See Figure 7.)

Figure 7: Growth in the Application of Toxic Effect Biomarkers Against Current % Share of Trials Within the Same Therapy Area



Confirming our analysis at the global level earlier, we see some areas of very strong growth in the utilization of disease markers (>100%). Within the utilization of disease markers, we see that gynecology and obstetrics uses disease markers at a higher level than any of the other TAs represented here; conversely, it is also displaying the lowest level of growth in utilization. Neurological disease, starting from a low base, is experiencing a huge rise in disease marker investment as it has in the other categories. (See Figure 8.)

Figure 8: Growth in the Application of Disease Biomarkers Against Current % Share of Trials Within the Same Therapy Area



The analysis we have shown here provides a macro view of an industry which has many individual successes and many ongoing challenges. Combining our awareness of the different biomarker roles and therapy areas, we can clearly confirm that applications of biomarkers for therapeutic effect, toxic effect and disease are all rising. However, the level of current use and investment varies considerably across different therapy areas reflecting different clinical strategies and confidence in the underlying biological fundamentals.

The importance of confidence in the underlying biological rationale is critical given the increasing duration and cost of conducting clinical trials. Biomarkers play a key role in the selection of patients and the ability to sufficiently demonstrate efficacy. In this analysis, we have demonstrated some strong and some weaker areas of growth. Neurological disease appears in the highest growth position in all three biomarker roles that we examined. Given that neurological disease is a relatively mature area, this represents a continued and increasing confidence in the role of biomarkers for therapeutic effect, toxic effect and disease. Nutritional disorder, despite having a much lower base of trial volume, is demonstrating our second highest growth in all categories except disease markers. Overall use of biomarkers within musculoskeletal disease trials also performs well across the tables. Despite the much celebrated successes that have propelled the potential appreciation in the role of biomarkers in neoplasm/oncology, growth is slowing and it does not appear near the top of any of the growth metrics.

Source: *Cortellis Clinical Trials Intelligence, Clarivate Analytics, March 2017.c.*

Who we are

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04.2017

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The Incidence and Prevalence Database of Clarivate Analytics

If everyone with rare diseases lived in one country, it would be the world's 3rd most populous country. Yet for many, rare diseases remain a mystery.

SHYAMA GHOSH, PH.D.,

Incidence and Prevalence Database Writer, IP & Science, Thomson Reuters

A young patient suffering from the rare disease MPS1-HS blogged "My main reason for sharing comes from wishing when I was diagnosed that there had been someone like me out there, especially another young adult, blogging about their experiences." The Incidence and Prevalence Database of Thomson Reuters enables new understanding of rare diseases, by describing the epidemiology of the most common rare disease in its database. This whitepaper endeavors to raise awareness for these conditions, by elaborating on the number of affected patients worldwide, the causes for these diseases, the aid obtained from patient advocacy organizations and rare disease-specific organizations, and the current market scenario regarding rare diseases.

How Many Are Affected?

Feb. 29, 2016 marked the 9th annual commemoration of the international Rare Disease Day. Currently, there are approximately 7,000 different types of rare diseases and disorders affecting about 350 million people worldwide. In the US, about 30 million people suffer from rare diseases (1 in 10 Americans or 10% of the U.S. population), and another 30 million people are living with rare diseases in Europe.

International definitions for rare diseases vary. In the US, a condition is considered "rare" when it affects fewer than 200,000 persons combined in a particular rare disease group. In the UK, a disease is considered rare if it affects fewer than 50,000 people. Some conditions initially classified as rare eventually outgrow this categorization (e.g., AIDS emerged in the United States as a rare disease, affecting fewer than 200,000 individuals, but spread

to nearly 470,000 by 2007, with the number of HIV-infected individuals exceeding 1.1 million in 2009). Whereas effective but non-curative treatment can turn a rare disease into a common one, effective prevention can, conversely, turn a common condition into a rare disease, as is observed for many once-common childhood infections such as mumps and measles.

With this backdrop, the study of rare diseases—in particular, the prevalence (number of people affected at any one time), incidence (number of new cases in a given year), and pattern of the disease (e.g., age distribution) reported for a particular population—may be somewhat inexact over time.

The prevalence distribution of rare diseases is skewed. Of the roughly 7,000 rare diseases known to date, an estimated 350 rare diseases are responsible for affecting 80% of all rare disease patients. The rarity of such conditions is exemplified by studying the prevalence data on fibrodysplasia ossificans progressiva (FOP), a rare disease where the patients' muscles and tendons are replaced by bone. FOP affects about 3,300 people worldwide, or approximately 1 in 2 million people. Such statistics may be better grasped by the following example: if a large football stadium holds 100,000 fans, one would need to fill nearly 20 football stadiums to find 1 person who has FOP. At the present time, researchers are aware of approximately 700 people throughout the world who have FOP.

Approximately 50% of people affected by rare diseases are children, with 30% of children with rare disease not surviving their 5th birthday. Rare diseases are responsible for 35% of deaths in the first year of life. Osteogenesis imperfecta (OI), also known as brittle bone disease, affects males and females in equal numbers. Untreated individuals often suffer from hundreds of fractures, and have a severe short stature. In the US, OI type I is estimated to occur in 1 in 30,000 live births, whereas OI type II is estimated to occur in 1 in 60,000 live births. The overall prevalence of all types of OI is estimated at .5 per 10,000 individuals in the US, with approximately 20,000 to 50,000 individuals in the country suffering from this rare disease.

In Europe, Sweden has reported dominant mutations in collagen type I that are responsible for 90% of OI cases, while OI type III is the most severe type compatible with surviving the neonatal period. The country reports a point prevalence of OI at birth anticipated to be close to 10/100,000.

For further information on this and other rare diseases, see the Incidence & Prevalence Database, by Thomson Reuters.

What Causes Rare Diseases?

While patients and families struggle to grasp the meaning and impact of a rare disease diagnosis, epidemiological and molecular research point to a large number of these diseases caused by genetic defects. Up to 80% of rare diseases are genetic in origin, and thus are present throughout a person’s life even if symptoms do not immediately appear. The Orphan Drug Act, the Rare

Diseases Act, and other policy initiatives have focused attention, resources, and incentives on the study of rare conditions and products to treat them.

However, understanding the genetic, infectious, or other cause of a disease does not necessarily mean that researchers understand the mechanism of the disease. The rare disease community knows little about von Hippel-Lindau (VHL) syndrome, even though mutations in the VHL gene have been identified as the cause and another gene has been implicated in disease variations. More common rare diseases such as cystic fibrosis and sickle cell disease have known causes and reasonably well-understood mechanisms but lack cures, satisfactory treatments, or preventive strategies.

Some rare conditions have multiple causes. Some forms of aplastic anemia, which is caused by damage to stem cells in the bone marrow and is diagnosed in about 500 to 1,000 people each year in the US, are inherited (e.g., Fanconi anemia). More often, though, the condition is acquired as a result of a toxic exposure (e.g., benzene, chloramphenicol), an infection (e.g., hepatitis, herpes virus), radiation or chemotherapy, or another disease (e.g., rheumatoid arthritis). This makes it difficult for the physician to determine the exact cause for a specific patient.

For certain rare diseases that have been named and characterized for decades, investigators still have not determined the cause. Whereas the disease was identified decades ago, no cause is reported for Gorham's disease, an extremely rare bone disorder that has been described under more than a dozen different names. The Vasculitis Research Consortium, which is part of the NIH-funded Rare Diseases Clinical Research Network, is investigating 6 forms of vasculitis (a group of rare conditions affecting blood vessels) for which the causes are not known.

What are Patient Advocacy Organizations?

“He looks like a perfectly normal child. You would never know that he is fighting daily for his life.”

- Mother of a patient suffering from juvenile dermatomyositis.

It takes the coming together of researchers, patients, caregivers and advocacy groups to raise disease awareness, especially when the disease is a rare one. By sharing individual case histories, patients, families, and caregivers form the basis for patient advocacy organizations that can advance drug development for rare indications into clinical development. Drug developers can benefit from access to such identified groups of patients, since it provides a pool of specific patients to register for clinical trials, for example. This is particularly important for rare diseases, where a lack of access to patients creates a significant hurdle in getting a new drug to market.

Western biopharma companies often have well-established relationships with patient groups in their focus area and provide significant levels of funding. In the US, the momentum to keep the research on rare diseases moving forward

is crucial. The 21st Century Cures Act, passed by the US House of Representatives last year, spoke of integrating the patient's opinion when designing clinical trials for rare diseases. Companies such as Ionis Pharmaceuticals, Inc. have joined hands with the Amyloidosis Research Consortium, Cure SMA, and Myotonic Dystrophy Foundation to raise awareness of those living with rare diseases, as have other organizations worldwide.

How are Rare Disease-Specific Foundations helping?

If everyone with rare diseases lived in one country, it would be the world's 3rd most populous country. Approximately 50% of rare diseases do not have a disease-specific foundation supporting or researching their cause. The Kakkis EveryLife Foundation has reported that up to 95% of rare diseases do not have a single FDA-approved drug treatment. In the 25 years since the Orphan Drug Act was passed (in 1983), only 326 new drugs were approved by the FDA and brought to market for all rare disease patients combined. According to the National Institutes of Health Office of Rare Disease Research, approximately 6% of the inquiries made to the Genetic and Rare Disease Information Center (GARD) are in reference to an undiagnosed disease.

It is a relatively recent phenomenon for pharmaceutical companies to strategically focus research and drug development in the field of rare diseases. Last year, up to half of the 45 FDA-approved new molecular entities targeted orphan indications. Organizations such as Global Genes, founded in 2008, are dedicated to helping families affected by rare disease and building a global network that promotes and supports the needs of the rare disease community. A growing pipeline of more than 460 orphan drugs is currently in development, which has boosted efforts in drug development and the understanding of rare diseases. Findacure, a UK-based charity, aims to build the rare disease community to drive research and develop treatments. In collaboration with Elsevier R&D Solutions, their mission will be to identify drug repurposing candidates for the rare disease congenital hyperinsulinism.

The Market Scenario

The recent boom in pharmaceutical mergers and acquisitions continues this year after the healthcare sector recorded its highest deal-making streak in history in 2015, with global transactions totaling $673 billion according to data from Thomson Reuters. This year, the pending takeover of Baxalta, Inc. by Shire plc. will create a world leader in rare diseases, with a focus on hematology, immunology, neuroscience, lysosomal storage disorders, gastrointestinal and endocrine disorders, hereditary angioedema, oncology and ophthalmology. Up to 60 programs are in the planning for clinical development, of which more than 50 have orphan drug status.

In the field of hemophilia alone, Baxalta is providing the recombinant Factor VIII product Advate (octocog alfa), recombinant human Factor VIII Recombinate, Obizur (susoctocog alfa/recombinant porcine factor VIII), and its long-acting PEGEGylated recombinant Factor VIII protein Adynovate, BAX-

817, BAX-826, and BAX-888. In parallel, the US has launched Biogen's long-acting product Eloctate (efmoroctocog alfa) in July 2014, and Roche's experimental antibody ACE-910 is likely to arrive by late 2017 or 2018. According to Consensus data from Thomson Reuters Cortellis for CI, sales of Eloctate and ACE-910 are to reach $667.8 million and $852.7 million, respectively, in 2021 (versus $1.245 billion and $600.0 million for Advate and Adynovate, respectively).

The Incidence and Prevalence Database: New Emphasis on Rare Diseases

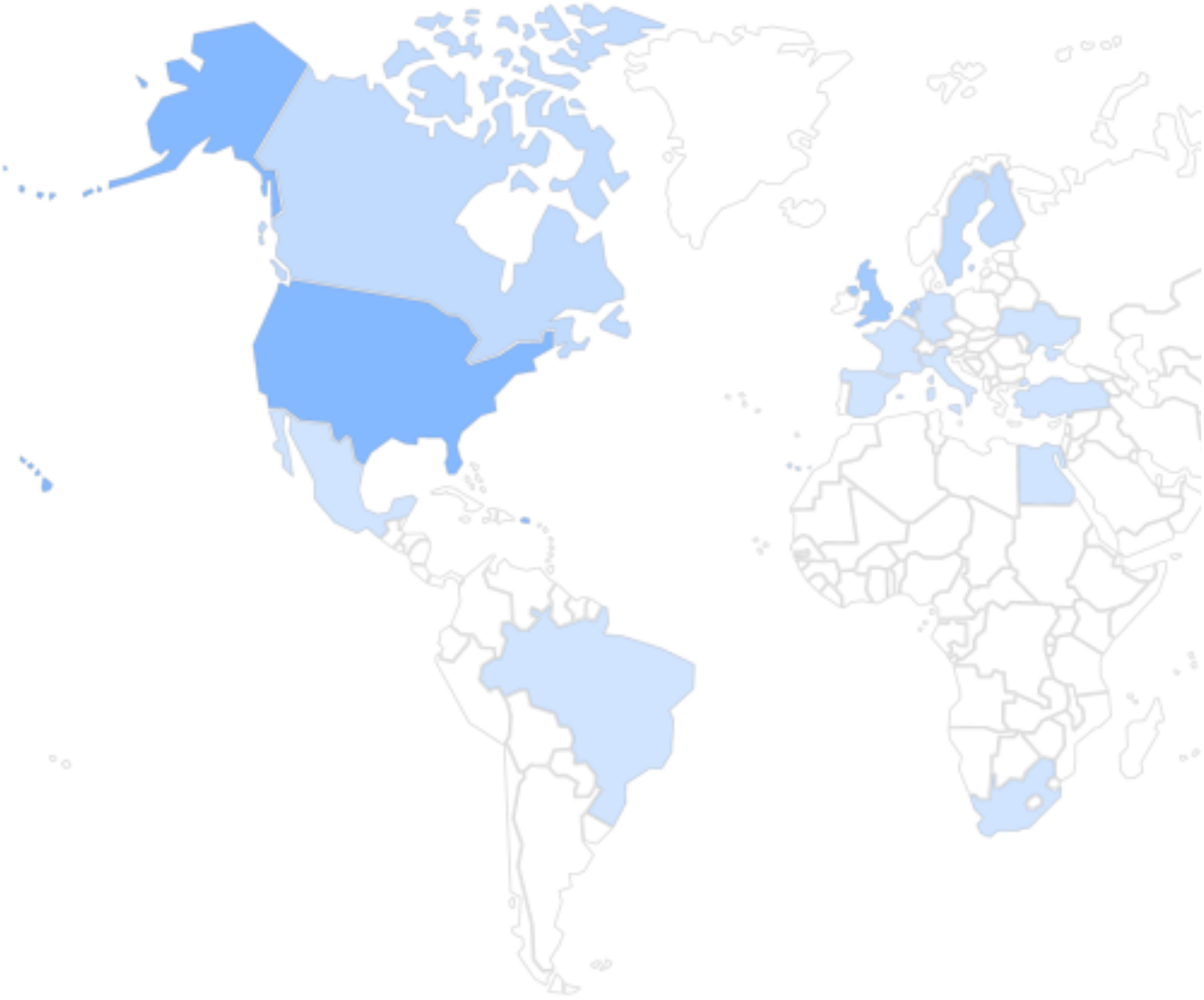

FIGURE 1: *Hemophilia A: Countries/regions with the most published epidemiology data available in the IPD*

The Incidence and Prevalence Database (IPD) is Thomson Reuters' tool for evaluating the world's epidemiology data. The IPD covers over 4,500

diseases, procedures, symptoms and other health issues for incidence, prevalence, morbidity, mortality, comorbidity, treated or diagnosed rates, cost and much more. The IPD is now presenting epidemiological data on rare diseases in the form of Article Reviews and IPD Summaries. Within the Article Reviews, specific information on the incidence, prevalence, morbidity and mortality of rare conditions are reported. IPD Summaries present tables of worldwide and regional incidence and prevalence data for the top rare diseases.

The diseases currently studied involve lysosomal storage disorders (Gaucher disease, Hunter Syndrome [mucopolysaccharidosis II], Fabry disease [Anderson-Fabry disease]), prion diseases (Creutzfeldt-Jakob disease), Zika virus disease, primary immunodeficiency, gastrointestinal/endocrine disorders (short bowel syndrome, Graves' disease), ophthalmological disorders (dry eye disease, conjunctivitis, and retinopathy of prematurity), and hemophilia (Fig.1.). Several other rare diseases in the fields of hematology, oncology, central nervous system, and infectious diseases are in the pipeline for reporting at the IPD site.